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(54) Title: CRYSTALLINE ZIPRASIDONE HCl AND PROCESSES FOR PREPARATION THEREOF

(57) Abstract: Provided is crystalline ziprasidone HCl and processes for preparation thereof.

## CRYSTALLINE ZIPRASIDONE HCl AND PROCESSES FOR PREPARATION THEREOF

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### Cross Reference To Related Applications:

This application claims the benefit of U.S. provisional application Serial No. 60/475,806, filed June 3, 2003; U.S. provisional application Serial No. 60/487,913, filed July 16, 2003; U.S. provisional application Serial No. 60/494,970, filed August 13, 2003; U.S. provisional application Serial No. 60/528,346, filed December 9, 2003, and U.S. provisional application Serial No. \_\_\_\_\_; filed May 17, 2003, the contents of all of which are incorporated herein.

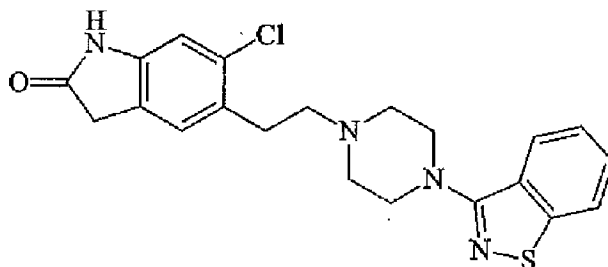
### Field of the Invention:

15 The present invention relates to the solid state chemistry of ziprasidone HCl.

### Background of the Invention:

Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. Ziprasidone has the following structure:

20



25

The preparation of ziprasidone base is disclosed in U.S. patent No. 4,831,031 (example 16). Preparation of ziprasidone base is also disclosed in U.S. patent No. 5,312,925. A process for preparation of ziprasidone HCl monohydrate having a mean particle size equal to or less than about 85 microns is also disclosed in U.S. Pat. No. 6,150,366 and EP  
30 0 965 343 A2.

Ziprasidone has been marketed under the name GEODON as an oral capsule and as an injectable drug. GEODON capsules contain the monohydrate hydrochloride salt of ziprasidone, and come in 20, 40, 60 and 80mg dosage forms. GEODON for injection

contains a lyophilized form of ziprasidone mesylate trihydrate, and contains 20mg base equivalent of ziprasidone. The mesylate salts of ziprasidone, including monohydrate and trihydrate, are disclosed in U.S. Pat. Nos. 6,110,918 and 5,245,765.

5 The present invention relates to the solid state physical properties of ziprasidone HCl. These properties can be influenced by controlling the conditions under which ziprasidone HCl is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered  
10 compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of  
15 dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medications. The solid state form of a compound may also affect its behavior on  
20 compaction and its storage stability.

Ziprasidone HCl has very low solubility in water (0.08 mg/ml). Increase in specific surface area (SSA) of low aqueous solubility materials may improve therapeutic activity (J. Phys. D: Appl. Phys. 26 (14 August 1993) B181-B187). The surface area of a solid  
25 material provides information about the void spaces on the surfaces of individual particles or aggregates of particles (EL Parrott, in Pharmaceutical Technology: Fundamental Pharmaceutics, Burgess, Minneapolis, Minn., 1970, pp 1-36). Factors such as chemical activity, adsorption, dissolution, and bioavailability of the drug may depend on the surface of the solid (EL Parrott, in Pharmaceutical Technology: Fundamental  
30 Pharmaceutics, Burgess, Minneapolis, Minn., 1970, pp 1-36, EL Parrott, Pharm. Manuf., 2, 30-37 (1985)). The adsorption of inert gases onto solid materials represents the most widely used method for the determination of SSA, although other methods are available (SL Lowell and JE Shields, Powder Surface Area and Porosity, Chapman and Hall New

York, 1984). The BET method (S. Brunauer, PH Emmett and E Teller, J. Am. Chem. Soc., 60, 309 (1938)) is generally used for gas adsorption surface area measurement.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. These conformational and orientational factors in turn result in particular intramolecular interactions and intermolecular interactions with adjacent molecules that influence the macroscopic properties of the bulk compound. A particular polymorphic form may give rise to distinct spectroscopic properties that may be detectable by powder X-ray diffraction, solid state  $^{13}\text{C}$  NMR spectrometry and infrared spectrometry. The polymorphic form may also give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others.

Ziprasidone HCl hemihydrate is disclosed in U.S. Pat. No. 4,831,031, Example 16 (column 13, line 13). A crystalline form of ziprasidone HCl (herein designated Form M) is disclosed in U.S. Pat. No. 5,312,925 and EP 0 586 181 A1. Form M is characterized by XRD, IR and water content. It is reported that the water content of Form M ranges from 3.8 to 4.5 % by weight, and that it is a monohydrate. Ziprasidone HCl Form M is prepared from ziprasidone base anhydrous.

The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. There is a need in the art for additional polymorphic forms of ziprasidone HCl.

### Summary of the Invention

In one aspect, the present invention provides for crystalline ziprasidone HCl, denominated Form A, characterized by data selected from the group consisting of a  
5 powder XRD pattern with peaks at 10.9, 17.4 and  $19.1 \pm 0.2$  degrees 2 theta and an FTIR spectrum with peaks at about 3400, 3344, 3172, 2949, 970, 940, 872 and  $843 \text{ cm}^{-1}$ .

In another aspect, the present invention also provides crystalline ziprasidone HCl form A, which consists of less than about 5% Form M.

10 In another aspect, the present invention also provides crystalline ziprasidone HCl form A, which does not transform to Form M by more than 5% upon heating.

In another aspect, the present invention also provides crystalline ziprasidone HCl form A, which does not transform to Form M by more than 5% upon storage at 0%  
15 humidity for 20 days or more.

In another aspect, the present invention also provides crystalline ziprasidone HCl form A, which does not transform to Form M by more than 5% upon storage at a temperature of between about  $25^\circ$  and  $55^\circ\text{C}$  for at least 3 months.  
20

In another aspect, the present invention also provides crystalline ziprasidone HCl form A, which has a specific surface area higher than about  $4\text{m}^2/\text{g}$ .

In another aspect, the present invention also provides crystalline ziprasidone HCl  
25 form A, which has high crystallinity.

In another aspect, the present invention provides a process for preparing crystalline ziprasidone HCl form A comprising:

- 30 a) providing a slurry of ziprasidone base, aqueous HCl and a solvent selected from the group consisting of toluene, monochlorobenzene, methanol, ethanol, diethyl-carbonate, water, isopropyl alcohol and mixtures thereof;
- b) maintaining the slurry to obtain crystalline ziprasidone HCl; and
- c) recovering the crystalline ziprasidone HCl.

In another aspect, the present invention also provides a process for preparing crystalline ziprasidone HCl form A comprising:

- a) dissolving, while stirring, ziprasidone base in a mixture of C<sub>1-4</sub> alcohol and an organic acid;
- 5       b) adding water and aqueous HCl to the solution;
- c) recovering the crystalline ziprasidone HCl.

In another aspect, the present invention also provides a process for preparing crystalline ziprasidone HCl form A, comprising:

- 10       a) providing a slurry of ziprasidone HCl characterized by a powder XRD pattern of 7.4, 13.0, 20.7, 23.4, 25.9  $\pm$  0.2 degrees 2 theta in THF or ethanol;
- b) maintaining the slurry to obtain the crystalline ziprasidone HCl; and
- c) recovering the crystalline ziprasidone HCl.

15       In another aspect, the present invention provides a process for preparing crystalline ziprasidone HCl form A comprising exposing ziprasidone HCl characterized by a powder XRD pattern of 7.4, 13.0, 20.7, 23.4, 25.9  $\pm$  0.2 degrees 2 theta to a relative humidity of about 20% to about 60%;

20       In another aspect, the present invention provides a process for preparing crystalline ziprasidone HCl form A substantially free of ziprasidone HCl Form M comprising:

- a) preparing a slurry of ziprasidone HCl in water, optionally in the presence of an organic solvent, at a temperature of about 0°C to about 40°C;
  - 25       b) maintaining the slurry to obtain the crystalline ziprasidone HCl; and
  - c) recovering the ziprasidone HCl.
- wherein the slurry is prepared by combining aqueous HCl in less than about 30 minutes with ziprasidone base in water.

30       In another aspect, the present invention provides a process for preparing ziprasidone HCl Form M comprising heating a slurry of the crystalline ziprasidone HCl Form A in ethanol.

In another aspect, the present invention provides a solid crystalline ziprasidone HCl having a water content of about 4.6% to about 6.6% by weight.

In another aspect, the present invention provides a process for preparing a solid  
5 crystalline ziprasidone HCl having a water content of about 4.6% to about 6.6% by weight comprising maintaining a slurry of ziprasidone HCl Form E in THF at a temperature below about 40°C.

In another aspect, the present invention provides a process for preparing a solid  
10 crystalline ziprasidone HCl having a water content of about 4.6% to about 6.6% by weight comprising maintaining a slurry of ziprasidone HCl Form E in THF at a temperature below about 40°C, drying solid obtained from the slurry at elevated temperature, contacting the solid with humid air to obtain the desired water content.

In another aspect, the present invention provides a solid crystalline ziprasidone  
15 HCl having a water content of about 4.6% to about 6.6% by weight which does not transform to Form M by more than 5% upon storage at 0% humidity for 20 days or more.

In another aspect, the present invention provides a solid crystalline ziprasidone  
20 HCl having a water content of about 4.6% to about 6.6% by weight which does not transform to Form M by more than 5% upon storage at a temperature of between about 25° and 55°C for at least 3 months

In another aspect, the present invention provides for solid crystalline ziprasidone  
25 HCl having specific surface area higher than about 4m<sup>2</sup>/g.

Also provided are pharmaceutical compositions and a method of treating a patient suffering from schizophrenia.

30

### Figures

Figure 1 is an X-Ray powder diffractogram of crystalline ziprasidone HCl Form A

Figure 2 is an X-Ray powder diffractogram of high crystallinity ziprasidone HCl Form A, containing about 5% Form M.

Figure 3 is an X-Ray powder diffractogram of high crystallinity ziprasidone HCl Form A.

Figure 4 is an IR spectra of crystalline ziprasidone HCl Form A.

5 Figure 5 is an IR spectra of crystalline ziprasidone HCl Forms A and M.

Figure 6 is an IR spectra of crystalline ziprasidone HCl Forms A and M.

Figure 7 is an X-Ray powder diffractograms of crystalline ziprasidone HCl Form A before and after heating.

Figure 8 is an X-Ray powder diffractograms of crystalline ziprasidone HCl Form M before and after heating.

Figure 9 is an X-Ray powder diffractograms of crystalline ziprasidone HCl Form A before and after storage at 0% relative humidity.

Figure 10 is an X-Ray powder diffractograms of crystalline ziprasidone HCl Form M before and after storage at 0% relative humidity.

15 Figure 11 is a comparison of XRD patterns of crystalline Ziprasidone HCl Form A and Ziprasidone HCl Form M.

**Detailed Description of the Invention:**

As used herein, the term slurry refers to a heterogeneous mixture.

20

As used herein, the term reduced pressure refers to a pressure below about 1 atm, more preferably below about 100 mmHg.

In one aspect, the present invention provides for crystalline ziprasidone HCl, denominated Form A, characterized by data selected from the group consisting of an X-Ray diffraction pattern having peaks at about 10.9, 17.4 and 19.1  $\pm 0.2$  degrees 2 theta, substantially as depicted in figure 1, and an FTIR spectrum with characteristic absorption bands at about 3400, 3344, 3172, 2949, 970, 940, 872 and 843  $\text{cm}^{-1}$ , substantially as depicted in figures 4 and 5. Crystalline ziprasidone HCl Form A of the present invention may be further characterized by XRD peaks at 25.0 and 26.0  $\pm 0.2$  degrees two-theta, and may be further characterized by XRD peaks at 13.9, 20.6, 21.3, 21.8 and 23.0  $\pm 0.2$  degrees two-theta. The crystalline ziprasidone HCl Form A provided in the present



invention has a water content of about 0.5% to about 6.6% by weight, and may have high crystallinity, substantially as depicted in figures 2 and 3.

The FTIR spectra of Forms A and M are similar, however differences can be seen in the  
5 ranges of 3600-2800 and 1000-750  $\text{cm}^{-1}$ , substantially as depicted in figures 4 and 5.

Ziprasidone HCl Form A may exist with crystallinity level. Crystalline ziprasidone HCl  
Form A and high crystallinity ziprasidone HCl Form A have the same characteristic peaks  
in XRD. However the peak width at half height for high crystalline ziprasidone is smaller  
10 than for crystalline ziprasidone HCl Form A; the peaks for high crystalline ziprasidone  
are sharper and well defined, while in the crystalline ziprasidone the peaks are wider and  
less resolved.

The peak width at half height for the peak at  $10.9^\circ 2\theta$  is  $0.21^\circ$  for high crystalline  
15 ziprasidone, and  $0.30^\circ$  for crystalline ziprasidone. For the peak at  $17.4^\circ 2\theta$ ,  $0.25^\circ$  for high  
crystalline ziprasidone and  $0.48^\circ$  for crystalline ziprasidone. For the peak at  $19.1^\circ 2\theta$ ,  
 $0.20^\circ$  for high crystalline ziprasidone and  $0.30^\circ$  for crystalline ziprasidone. For the peak at  
 $23.0^\circ 2\theta$ ,  $0.37^\circ$  for high crystalline ziprasidone and  $0.54^\circ$  for crystalline ziprasidone.  
Preferably, the crystalline form has peaks with a higher than about the average width as  
20 illustrated (average of the two widths provided), more preferably higher than about 75%  
of the range of the two widths provided.

Some Peak width at half height for Crystalline ziprasidone HCl Form A and high  
crystallinity ziprasidone HCl Form A

Peaks $\pm 0.2$ degrees 2 theta	Peak width at half height for Crystalline ziprasidone HCl Form A (degrees 2 theta)	Peak width at half height for high crystallinity ziprasidone HCl Form A (degrees 2 theta)
10.9	0.30	0.21
17.4	0.48	0.25
19.1	0.30	0.20
23.0	0.54	0.37

25

The crystalline ziprasidone HCl Form A of the present invention may be substantially free from other crystalline forms, *i.e.* no more than about 5% of other crystalline forms, preferably Form M. A suitable technique for monitoring the crystalline content is X-Ray powder diffraction. In addition, no more than 5% of Form A transforms into Form M during heating and also during exposure to 0% relative humidity.

The crystalline ziprasidone HCl Form A of the present invention may be heated to a temperature of up to about 140°C without a change in the crystal structure (see table 1 and figure 7).

10

Table No.1

Crystalline ziprasidone HCl forms heated at 80-105°C overnight

Original crystal form	Crystal form after heating at 80-105°C overnight
Form A	Form A
Form M	Anhydrous

The present invention provides a crystalline ziprasidone HCl Form A, of which no more than about 5% is transformed into Form M upon exposure at 0% humidity for prolonged periods (such as 3 weeks, see table 6 and figure 9), or storage under accelerated aging conditions (such as 40°C, 75% RH, see tables 2 and 3) for at least about 6 months. Ziprasidone HCl Form M, however, converts to the anhydrous form under heating (see table 1 and figure 8) or exposure to 0% relative humidity (see table 6 and figure 10).

20

Table No. 2

Stability results

Time Interval	Results		
	25°C	40°C	55°C
t=0	A		
1M		A	A
2M		A	A
3M	A	A	A
6M	A	A	A

Table No. 3  
Stability results

Time Interval	Results		
	25°C	40°C	55°C
t=0	A+ less than 5%M		
1M		A+ less than 5%M	
2M		A+ less than 5%M	A+ less than 5%M
3M	A+ less than 5%M	A+ less than 5%M	A+ less than 5%M
6M	A+ less than 5%M	A+ less than 5%M	A+ less than 5%M

- 5 When slurried in water, no more than 5% Form A is transformed into Form M. However, in ethanol slurry, 95% of the crystalline ziprasidone transforms to Form M.

The crystalline ziprasidone HCl Form A provided in the present invention has a specific surface area (SSA) higher than about 4m<sup>2</sup>/g, more preferably higher than about 8, most  
 10 preferably higher than about 11 such as about 14 as measured by BET. Preferably, the SSA is about 5 to about 20 m<sup>2</sup>/g. The high SSA of the crystalline ziprasidone HCl is achieved by the rapid addition of HCl to the solution of ziprasidone base, and precipitation at a low temperature. The results are summarized in Table 4:

Table No. 4  
Specific surface area results

Sample	Specific surface area [m <sup>2</sup> /g]	Crystal form
** Repetition of US 6,150,366 Example10	2.135	M
** Repetition of US 6,150,366 procedure (comparative example 15)	3.908	M
** Repetition of US 5,312,925 Example 2	3.909	M
** Sample prepared according to example 16	5.461	A
** Sample prepared according to example 19	11.335	A
* Sample prepared according to example 17	14.646	A
* Sample prepared according to example 18	18.831	A

\* cell volume= 12 cm<sup>3</sup>

\*\* cell volume= 9 cm<sup>3</sup>

The crystalline ziprasidone HCl Form A provided in the present invention has a  
5 significantly higher specific surface area than Form M prepared by repeating the  
procedure disclosed in US Pat. No. 5,312,925 and Example 10 in US Pat. No. 6,150,366.

Crystalline ziprasidone HCl Form A may be prepared by providing a slurry of ziprasidone  
base, aqueous HCl and a solvent selected from the group consisting of toluene,  
10 monochlorobenzene, methanol, ethanol, diethyl-carbonate, water, isopropyl alcohol or  
mixtures thereof, and allowing the slurry to last for a sufficient time (maintaining) to  
obtain crystalline ziprasidone HCl Form A. When the solvent is a non-polar solvent or  
water, the combining/reacting is preferably carried out at a temperature of at least about  
40°C, more preferably from about 50°C to about 70°C, and most preferably at about  
15 60°C. The combining with HCl is preferably carried out rapidly. The slurring after the  
combining is preferably carried out at a temperature of about 20°C to about 30°C, more  
preferably at about room temperature. Form A obtained by this process may have high  
crystallinity.

20 Crystalline ziprasidone HCl Form A can also be prepared by stirring a solution of  
ziprasidone base, a C<sub>1-4</sub> alcohol and an organic acid (such as a C<sub>1</sub> to C<sub>7</sub> carboxylic acid) at  
room temperature, then adding water and aqueous HCl to obtain crystalline ziprasidone  
HCl Form A. Preferably, the C<sub>1-4</sub> alcohol is either ethanol or methanol. Preferably, the  
organic acid is a C<sub>1-4</sub> carboxylic acid, more preferably the organic acid is acetic acid and  
25 formic acid.

The water content of crystalline ziprasidone HCl Form A can be increased by  
humidification.

30 Crystalline ziprasidone HCl Form A may also be prepared by slurring another form of  
ziprasidone HCl in a suitable solvent such as tetrahydrofuran or ethanol. Preferred  
starting material is ziprasidone HCl Form E. The slurry is allowed to last for a sufficient  
time to obtain crystalline ziprasidone HCl, which may be recovered by techniques well

known in the art such as filtration. The slurry temperature is preferably at least about 40°C when using THF. Ziprasidone HCl Form E transforms to Form A when exposed to a relative humidity of about 20% to about 60% for about 22 days.

- 5 Ziprasidone HCl having a water content of about 4.6% to about 6.6% may be prepared by slurry of ziprasidone HCl Form E in THF. The temperature of the slurry is preferably less than about 40°C, more preferably about room temperature. The slurry is maintained preferably of about 12 hours to about 3 days. The wet solid may then be dried, for example at a temperature of about 40°C to about 70°C, followed optionally by additional  
10 drying up to a temperature of preferably about 120°C, as illustrated in examples 20 and 21. The solid, if dehydrated, may then be put in a humid atmosphere, preferably more than about 50% humidity, more preferably more than about 80% humidity and most preferably about 100% humidity to obtain a hydrated crystal having a water content of about 4.6% to about 6.6% by weight.

- 15 Ziprasidone HCl Form M may be prepared by slurring Form A in a C<sub>1</sub> to C<sub>4</sub> alcohol or acetic acid, preferably ethanol (preferably 95%), more preferably at a temperature of about reflux temperature and 20°C below the reflux temperature, even more preferably about 10°C below the reflux temperature to about reflux, and most preferably at about  
20 reflux temperature. About three hours at reflux temperature is sufficient to obtain a transformation.

- The present invention also provides for preparing crystalline ziprasidone HCl Form A by exposing ziprasidone Form E to a relative humidity of about 20% to about 60% for about  
25 22 days (see table 5).

Table No. 5

Water uptake (%) and crystal form of ziprasidone HCl form E equilibrated at different relative humidities for 22 days

RH (%)	TGA weight loss (%)	Crystal form
0	5.3	Amorphous

20	7.2	A
40	4.8	A
60	5.0	A
80	9.2	M + A
100	51.3	M + A+ amorphous

The present invention also provides for preparation of substantially pure crystalline ziprasidone HCl Form A. In this embodiment, crystalline ziprasidone HCl is prepared by fast crystallization through addition of HCl to a slurry or solution of ziprasidone base in a solvent such as water, a C<sub>1</sub> to C<sub>4</sub> linear or branched alcohol, or mixtures thereof. An IPA/water ratio of about 2:1 to about 0:20 (v/v) is an appropriate solvent for preparation of substantially pure crystalline ziprasidone HCl Form A. Suitable temperature for the reaction is from about 0°C to about 40°C. A suitable HCl quantity is from about 2 to about 8 equivalents. Preferably, the HCl is added at a fast rate. The addition rate is temperature related: at room temperature, the rate is preferably about 5 to about 30 minutes, more preferably about 5 to about 20 minutes, most preferably about 5 to about 10 minutes; at a lower temperature, the addition rate is preferably about 5 to about 60 minutes, more preferably about 5 to about 30 minutes. The addition may also be carried out in reverse, *i.e.*, addition of ziprasidone base slurry/solution to HCl.

One of skill in the art would appreciate that as the slurry is allowed to last for a sufficient time to obtain a particular polymorphic form, the slurry may dry up due to for example evaporation of the solvents. As the examples illustrate, additional amounts of a solvent may be added (same or different solvent), preferably followed by stirring, to obtain a slurry.

A slurry is most effective when the solids of the heterogeneous mixture are in substantial contact with the solvent. When the solids settle down, the efficiency of the slurry process often decreases due to a decrease in contact. Thus, one of skill in the art would appreciate that if during the slurry process the solids settle down, a force such as stirring or agitating may be applied to disperse the solid. Even when the solids have not settled down,

bringing of movement in the solvent may even further increase the efficiency of the slurry process.

Crystalline ziprasidone HCl Form A may be recovered from the slurry by conventional techniques in the art such as decanting, filtration and centrifugation.

The present invention also provides solid crystalline ziprasidone HCl having a water content of about 4.6% to about 6.6% by weight. This crystalline form may be sesquihydrate. No more than 5% of the solid crystalline ziprasidone HCl of the present invention transforms into Form M during exposure to 0% relative humidity (see table 6). The present invention further provides a solid crystalline ziprasidone HCl, of which no more than 5% transforms into Form M upon storage at 25, 40 and 55°C for at least 3 months, preferably for at least 6 months (see table 7). This solid crystalline ziprasidone HCl has a specific surface area (SSA) higher than 4m<sup>2</sup>/g, and preferably between 5 and 20 m<sup>2</sup>/g.

**Table No.6**

Water uptake (%) and crystal form of crystalline ziprasidone HCl forms equilibrated at 0% relative humidity

Original crystal form	Crystal form upon storage at 0% relative humidity
Form A	Form A
Crystalline ziprasidone HCl having a water content of 4.6-6.6%	Crystalline ziprasidone HCl having a water content of 4.6-6.6%
Form M	Anhydrous

20

**Table No. 7**

Stability results

Time Interval	Results		
	25°C	40°C	55°C

<u>t=0</u>	Cryst. ZPR HCl (4.6-6.5% water)		
<u>1M</u>		Cryst. ZPR HCl (4.6-6.5% water)	Cryst. ZPR HCl (4.6-6.5% water)
<u>2M</u>		Cryst. ZPR HCl (4.6-6.5% water)	Cryst. ZPR HCl (4.6-6.5% water)
<u>3M</u>	Cryst. ZPR HCl (4.6-6.5% water)	Cryst. ZPR HCl (4.6-6.5% water)	Cryst. ZPR HCl (4.6-6.5% water)
<u>6M</u>	Cryst. ZPR HCl (4.6-6.5% water)	Cryst. ZPR HCl (4.6-6.5% water)	Cryst. ZPR HCl (4.6-6.5% water)

Pharmaceutical formulations of the present invention contain crystalline ziprasidone HCl, such as one of those disclosed herein, or ziprasidone HCl amorphous, optionally in mixture with other form(s) of ziprasidone. In addition to the active ingredient(s), the pharmaceutical formulations of the present invention may contain one or more excipients. Excipients are added to the formulation for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum



silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon<sup>®</sup>, Plasdone<sup>®</sup>), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol<sup>®</sup>, Primellose<sup>®</sup>), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon<sup>®</sup>, Polyplasdone<sup>®</sup>), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrifin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab<sup>®</sup>) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

- 5 In liquid pharmaceutical compositions of the present invention, ziprasidone and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse  
10 uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

15

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose,  
20 ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

- 25 Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at  
30 levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate,

sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

5 The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred  
10 route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

15 The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

20 The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet  
25 granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

30 A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a

sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly  
5 into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with  
10 experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

15

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will  
20 depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

The dosage of GEODON may be used as guidance. The oral dosage form of the present  
25 invention is preferably in the form of an oral capsule having a dosage of about 10 mg to about 160 mg, more preferably from about 20 mg to about 80 mg, and most preferably capsules of 20, 40, 60 and 80 mg.

#### **Instrumentation:**

30

X-Ray powder diffraction data were obtained using by method known in the art using a SCINTAG powder X-Ray diffractometer model X'TRA equipped with a solid state

detector. Copper radiation of 1.5418 Å was used. A round aluminum sample holder with round zero background quartz plate, with cavity of 25(diameter)\*0.5(dept) mm. Detection limit: 5%.

5 TGA analysis was done using a Mettler M3 meter. The weight of the samples was about 10 mg; the samples were scanned at a rate of 10°C/min from 25°C to 200°C. The oven was constantly purged with nitrogen gas at a flow rate of 40 ml/min. Standard 70 µl alumina crucibles covered by lids with 1 hole were used.

10 IR analysis was done using a Perkin Elmer SPECTRUM ONE FT-IR spectrometer in DRIFT mode. The samples in the 4000-400 cm<sup>-1</sup> interval were scanned 16 times with 4.0 cm<sup>-1</sup> resolution.

The water content of ziprasidone HCl was measured by the methods known in the art like  
15 Karl Fisher or thermogravimetric analysis (TGA). The TGA of the crystalline ziprasidone HCl matched with the Karl Fisher analysis. Water content is measured as percent w/w.

Specific surface area measurement:

20 Instrument: Coulter SA3100

Degassing: without

Sensitivity: high

Calculation: BET

Type: multipoint

25 Points: 10

Sample cell: 9 and 12cm<sup>3</sup>

Ziprasidone free base used for preparations of the crystal forms of ziprasidone HCl may be, but is not limited to Form B. Ziprasidone base Form B is characterized by X-Ray  
30 peaks at 12.1, 15.2, 16.3, 18.4, 25.0 degrees 2 theta and is further characterized by XRD peaks at 5.2, 10.4, 11.3, 13.1, 21.1, 22.1. The ziprasidone free base has a DSC thermogram in which 17 and 120 J/g endothermic peaks can be seen at 92 and 220°C. The first corresponds to dehydration, the second to melting of the ziprasidone free base. The

water content of the sample of the base is about 1.2 % by weight. The Loss on Drying by TGA is about 2.1 % by weight. One of skill in the art would appreciate that the processes of the present invention may use other forms of ziprasidone base as starting material.

5

### Examples

#### Example 1- Preparation of Ziprasidone base

Ziprasidone base for the experiments below was prepared according to the procedure "EXPERIMENT" in US Pat. No. 5,312,925, column 4. The water content of the base  
10 was 1.2 % (Karl Fisher).

#### Example 2- Preparation of Ziprasidone base Form B

Ziprasidone base (50g) and toluene (250ml) were charged into a 0.5 L three necked flask. The obtained slurry was heated at 85°C for 2 hours. The hot slurry was filtrated and the  
15 solid was washed with methanol. The solid was dried in air-circulated oven at 50°C to afford the dried Ziprasidone base form B (by XRD) (45.39g).

#### Example 3- Preparation of crystalline ziprasidone HCl Form A in toluene from ziprasidone base form B and aqueous HCl.

20 Ziprasidone base Form B (10g) and toluene (200ml) were heated to reflux, and the slurry was cooled to ~65°C. At 65°C, aqueous HCl 37% (10ml) was added and the slurry was stirred at room temperature over night. The solid was a sticky material; to which water was added (100ml). The solid was then filtered and washed with toluene. The wet solid was crystalline ziprasidone HCl as confirmed by XRD. The product was dried in an oven  
25 at 50°C. The dried solid was crystalline ziprasidone HCl Form A, (10.64g) as confirmed by XRD. (The water content was 4.7% by K.F.).

#### Example 4- Preparation of crystalline ziprasidone HCl Form A in monochlorobenzene/methanol from ziprasidone base form B and aqueous HCl

30

To a slurry of ziprasidone base Form B (10g) in monochlorobenzene (100ml) was added aqueous HCl (37%) (10ml) at room temperature and the stirring was continued at room temperature over night. A sticky solid was formed, to which methanol (50ml) was added, followed by stirring for an additional 4 hours. The solid was filtered and washed with

methanol. The wet product was crystalline ziprasidone HCl as confirmed by XRD. After drying at 50°C for about 16 hours, crystalline ziprasidone HCl Form A was obtained (10.37g) as confirmed by XRD (The water content was 4.17% by K.F.).

5 **Example 5- Preparation of crystalline ziprasidone HCl Form A in water from Ziprasidone base form B and aqueous HCl 3M.**

Ziprasidone base Form B (10g) was added to a 3M solution of HCl (50ml HCl (37%) in 150ml HPLC grade water) and the slurry was heated at 60°C. The reaction mixture was then stirred at 60°C for 18hours. After cooling to room temperature, a solid was filtered  
10 and washed with water. The material was dried in an oven at 50°C for 16 hours. The wet solid and the dried solid were crystalline ziprasidone HCl Form A (the water content of the dried solid is 4.88% by K.F.), as confirmed by XRD.

15 **Example 6- Preparation of crystalline ziprasidone HCl Form A in isopropyl alcohol from Ziprasidone base form B and aqueous HCl**

Hydrochloric acid (37%) (10ml) was added to a slurry of ziprasidone base Form B in isopropyl alcohol (IPA) ( 100ml). The slurry was stirred at room temperature over night. A solid was filtered, washed with IPA and dried at 50°C for 16hours. The dried solid was crystalline ziprasidone HCl Form A (The water content of the dried solid is 4.01% by  
20 K.F.), as confirmed by XRD.

**Example 7- Preparation of Ziprasidone HCl form E from Ziprasidone base form B in acetonitrile and aqueous HCl**

Aqueous HCl (37%) (10ml) was added to a slurry of ziprasidone base Form B (10g) in  
25 acetonitrile (200ml) at reflux. After the addition, the slurry was heated over night. A solid was filtered and washed with acetonitrile. After drying at 50°C for ~16 hours, ziprasidone HCl Form E was obtained (12.71g) (The water content was 9.25% by K.F. and the loss on drying by TGA is 18.8%), as confirmed by XRD.

30 **Example 8- Preparation of Ziprasidone HCl monohydrate (M) from Ziprasidone HCl form A**

Crystalline ziprasidone HCl Form A (10g) was heated in ethanol 95% (200ml) at reflux for 3 hours. The hot slurry was filtered to obtain a solid. The solid was washed with hot

ethanol (10mlx4). Part of the wet solid was dried at 50°C for 16 hours and the other part at 45°C under vacuum. The wet and dried solids were ziprasidone HCl Form M (the monohydrate) (The water content of the dried solids was 4.25 and 4.24% (by K.F) and the loss on drying by TGA are 4.6%), as confirmed by XRD.

5

In all the above examples, drying was carried out in an air-circulated oven.

**Example 9- Preparation of crystalline ziprasidone HCl Form A by slurry of**

10 **ziprasidone HCl Form E**

1) Ziprasidone HCl Form E (2g) in ethanol 95% (20ml) was stirred at room temperature for 24 hours. A solid was filtrated, washed with ethanol (95%) and dried at 50°C in an air-circulated oven. The dried solid was crystalline ziprasidone HCl Form A (K.F. 5.16%).

15 The same result as was obtained when the temperature during the slurry was 50°C (K.F. 5.06%).

2) Crystalline ziprasidone HCl Form A was obtained by slurry of Form E in ethanol with various water contents (from 5% to 30%) (K.F. 5.16%) at room temperature or at 50°C (K.F. 5.06% and 4.99%) or by slurry of Form E in THF containing  
20 water at a temperature between room temperature and 50°C. For example, the slurry of E in THF containing 40% water at 50°C gave crystalline ziprasidone HCl Form A (K.F. 4.76%).

25 **Example 10- Preparation of crystalline ziprasidone HCl Form A with high crystallinity from ziprasidone base in diethyl-carbonate/aq. HCl**

To the slurry of ziprasidone base (10g) (Form B) in diethyl-carbonate (250ml) at 60°C was added concentrated aqueous HCl (10ml); then the slurry was stirred at room temperature for about 16 hours. Water (50ml) was added and the stirring  
30 was continued for an additional three hours. A solid was filtrated, washed with water (2x20ml) and dried in an air-circulated oven for 16 hours. The wet and the dried solid was crystalline ziprasidone HCl (K.F. 4.16%). The dried solid was Crystalline ziprasidone HCl Form A with high crytsallinity.



**Example 11- Preparation of substantially pure crystalline ziprasidone HCl Form A****1) Preparation of crystalline ziprasidone HCl from isopropyl-alcohol: water.**

In a 250ml reactor were charged ziprasidone base (10g) and a 1:1 mixture of isopropylalcohol-water (100ml), and the mixture was cooled to 10°C. To the above slurry, aqueous HCl (32%) was added during 5 minutes, while maintaining the temperature less than 15°C. The obtained slurry was than stirred at 10-15°C for 15 hours, and a solid was isolated by filtration, washed with IPA-water and dried at 50°C under vacuum. The XRD of the dried material (10.79g), which lacked the peak at 18.1, characteristic of Form M, indicates that the product was crystalline ziprasidone HCl Form A substantially free of Form M (water content by K.F. is 4.85%).

**2) Preparation of crystalline ziprasidone HCl Form A from water.**

To the slurry of ziprasidone base (10g) in water (100ml) at room temperature, aqueous HCl (10ml) (32%) was added over 10 minutes. The slurry was then stirred at room temperature for 5 hours. The solid was filtrated, washed with water and dried on table, followed by drying at 50°C. The XRD of the solid, which lacked the peak at 18.1, characteristic of Form M, showed the product was crystalline ziprasidone HCl Form A substantially free of Form M (water content by K.F. 5.04).

**3) Preparation of crystalline ziprasidone HCl Form A from IPA-water by reverse addition.**

A slurry of ZPR base (5g), 25 ml IPA and 25 ml water was prepared in a 250 ml reactor. This slurry was dropped into a flask containing (32%) aqueous HCl (10ml) at room temperature. During the addition, the temperature rose to ~35°C. The slurry was than stirred at room temperature 24 hours. The solid was filtrated, washed with mixture water-IPA and dried at 50°C. The XRD of the dried solid (7.2g), which lacked the peak at 18.1, showed the material was crystalline ziprasidone HCl Form A substantially free of Form M (water content by K.F. 4.89).

**Example 12- Preparation of form M from crystalline ziprasidone HCl Form A.**

The slurry of crystalline ziprasidone HCl Form A (30g) and acetic acid (510ml) was heated at 60°C for 2h. The mixture was then cooled to room temperature and the solid was filtrated and washed with acetic acid (2x30ml). After drying at 50°C ziprasidone HCl  
5 Form M was obtained (28.37g). (Water content by K.F. 3.95%).

**Example 13- Preparation of ziprasidone HCl Form A in humid air fluidized bed drier****1) Precipitation from solution**

10 60 gr of Ziprasidone-base Cryst, 480 ml of Ethanol 95% and 300 ml of Acetic Acid were fed into a 1 liter stirred glass beaker at 25°C. The stirrer was turned on, and the mixture was stirred for 20 min until the Ziprasidone-base dissolved completely. 6 gr of "Eno" type Active Carbon were fed into the beaker, and the solution was Carbon treated for 30 min at 25°C. The used Carbon was removed by  
15 filtering the treated solution under reduced pressure through a No.1 Whattman filtration paper.

The used carbon was washed with 120 ml 95% Ethanol, and the wash filtrate was added to the filtered solution, both were fed into a 1 liter stirred glass reactor. 300 ml of treated Water were added into the reactor, and the solution was cooled  
20 to 0°C. 120 ml 10% w/w aqueous Hydrochloric acid solution was added drop wise into the reactor during 10 min. During the acid addition, Ziprasidone-hydrochloride precipitated. After the acid addition was completed, the slurry was stirred at 0°C for additional 30 min.

The crystals were isolated by filtering the slurry under reduced pressure through a  
25 No. 1 Whattman filtration paper. After drainage of the mother liquor, The wet cake was washed with 120 ml aqueous mixture consisting of 50% Ethanol 95%. After the wash liquor was completely drained, the wet cake was washed with 300 ml of water. The wet filter cake was washed four additional times, each time with 300 ml (total 1500 ml) until pH~5 was obtained (the same pH as the pH of the  
30 fresh Water).

120gr of wet Ziprasidone-HCl crystals were obtained.

The wet crystals were tested by XRD and found to be ziprasidone HCl Form A.

The wet crystals were dried at 50°C for 60 hrs, until the water content was 0.75%.

2) Humidification

20gr of the dried product were humidified in a humid air fluidized bed drier ("Mini-Glatt"). The dry air inlet temperature was 50°C. After the water spray, the  
5 air temperature was 16°C.

After 30 min, the water content in the product was 5.77%

The humid product was discharged.

Example 14- Preparation of high crystallinity ziprasidone HCl Form A from

10 ziprasidone base in IPA/water/HCl

Into a 250ml flask were charged ZPR base (10g), water (50ml) and IPA (50ml). To the obtained slurry HCl 32% (20ml) was added during 0.5h. The temperature rose from room temperature to about 30°C. The stirring was continued for 20h at room temperature; after this the solid was filtrated, washed twice with a mixture IPA-water 1:1 (10ml) and dried  
15 in vacuum oven at 50°C. The dried solid was high crystallinity ziprasidone HCl Form A (by XRD). (The water content is 4.89 by K.F.)

Example 15- Comparative example: preparation of ziprasidone HCl Form M from THF: H<sub>2</sub>O (from US 6,150,366)

20 Into a 250 ml reactor, Ziprasidone base (3g), THF (90 ml) and H<sub>2</sub>O (9 ml) were charged. As the reactor was heated to reflux (64°C), Ziprasidone dissolved, forming a clear, dark solution. The temperature was lowered to 60°C and stirring to 103rpm. HCl 11% was added until turbidity was observed. This turbid solution was left under stirring at 60°C for 50 min., and the rest of 9g HCl 11% was added dropwise during 30 min.  
25 The slurry was cooled to 13°C, kept at this temperature for 1h 40 min., filtrated, and washed with two portions of 3ml THF. The solid was dried at 23°C overnight. The dried solid was crystalline ziprasidone HCl Form M (by XRD). Specific surface area 3.908 m<sup>2</sup>/g

30 Example 16- Preparation of ziprasidone HCl Form A from EtOH:H<sub>2</sub>O

A 150 ml reactor equipped with mechanic stirring was charged with Ziprasidone base (3g), EtOH abs. (15 ml) and H<sub>2</sub>O (15 ml), cooled to 15°C, and a slurry was obtained. slurry. HCl 21% (4.55 ml) were added dropwise during 10 min. After the addition the

slurry is left at the same temperature overnight. The slurry was then filtered, washed with EtOH:H<sub>2</sub>O (10 ml), and dried at 65°C under vacuum. The dried solid was crystalline ziprasidone HCl Form A (by XRD). Specific surface area: 5.461 m<sup>2</sup>/g

5    **Example 17- Preparation of ziprasidone HCl Form A from IPA: H<sub>2</sub>O at room temperature**

A 50ml flask equipped with mechanic stirring was charged with Ziprasidone (3.5 g), IPA (17.5 ml) and H<sub>2</sub>O (17.5 ml), and a slurry was obtained.

HCl 32% (3.33ml) was added dropwise during 2 min, and the temperature was raised  
10    from 25 to 29°C. After addition, the slurry was left overnight, while stirring. The slurry was then filtrated, washed with IPA: H<sub>2</sub>O 1:1 (7 ml) and dried at 65°C under vacuum. The dried solid was crystalline ziprasidone HCl Form A (by XRD). Specific surface area: 14.646 m<sup>2</sup>/g

15    **Example 18- Preparation of ziprasidone HCl Form A from IPA: H<sub>2</sub>O at 9°C**

A flask was charged with Ziprasidone (4.9 g), IPA (12.5 g) and H<sub>2</sub>O (12.5 g), and was cooled in ice bath. When the temperature reached 9°C, HCl 21% (7.7 ml) was added dropwise during less than 5 minutes. The temperature was raised to 13°C, and the slurry was left, while stirring, at room temperature overnight. The slurry was then filtered,  
20    washed with IPA and dried at 50°C under vacuum. The dried solid was crystalline ziprasidone HCl Form A (by XRD). Specific surface area: 18.831 m<sup>2</sup>/g.

**Example 19- Preparation of ziprasidone HCl Form A from Acetic acid/ethanol**

Ziprasidone base (11.2 g) was dissolved in EtOH (112 ml) and Acetic acid (78.2 ml). The  
25    solution was treated with active charcoal at 0°C for color improvement during 30 min and filtrated. The solution was cooled back to 0°C, and HCl 32% (10 ml) was added. 30 min after the addition, the slurry was filtered and the solid dried at 50°C under vacuum. The dried solid was crystalline ziprasidone HCl Form A (by XRD). Specific surface area: 11.335 m<sup>2</sup>/g.

30

**Example 20- Preparation of crystalline ziprasidone HCl having a water content of 4.6-6.6% by slurry of ziprasidone HCl form E**

Ziprasidone HCl Form E was stirred in tetrahydrofuran (20ml) at room temperature for 23 hours. A solid was filtrated, washed with THF and dried at 60°C in an air-circulated oven. The dried solid was crystalline ziprasidone HCl (K.F. 4.57%).

5 **Example 21- Preparation of ziprasidone HCl having a water content of 4.6-6.6% from Acetic acid/ethanol**

Crystalline ziprasidone HCl was prepared according to ex. 20. The wet solid was dried at 50°C for about 16 hrs in vacuum oven, followed by an additional drying operation in vacuum-oven at 105°C for 48 hrs. After drying, the solid contained 1.3% water (by Karl-  
10 Fischer).

The above dried material was kept in a chamber with RH 100% at 40°C for 7 days. After this period of time the water content was 6.6% (by Karl-Fischer).

**Example 22- Preparation of ziprasidone HCl Form A from Acetic acid/ethanol**

15 Ziprasidone base (15g) was dissolved in a mixture of ethanol (150ml) and acetic acid (75ml). The solution was treated with basic alumina (1.5g) for half hour. The discolored solution was filtrated and cooled to ~10°C. Aqueous HCl (10%, 30ml) was added during 3 min. at the chilled solution (10°C). The stirring was continued for additional 10 min. at 10°C. The obtained solid was filtrated, washed with water to pH 4 and dried in vacuum-  
20 oven at 50°C for about 4 days. The obtained dried solid contained 0.53% water (by K.F.).

**Example 23- Preparation of ziprasidone HCl Form A from AcOH/MeOH/water**

Ziprasidone base (5g) was dissolved in a mixture of acetic acid (25ml), methanol (47.5ml) and water (2.5ml); the obtained solution was treated with active carbon  
25 (10%w/w) and tonsil (10% w/w). The solution was filtrated, diluted with water (25ml) and cooled to 10°C. While the temperature reached 10°C 10% HCl was added (10ml) over 5 minutes. The stirring was continued for 40 min., then the solid was filtrated and washed with water and then with a mixture of MeOH/water. The solid obtained after drying was crystalline ziprasidone HCl form A.

30

Other similar procedures are shown in the following table:

AcOH= Acetic acid

Example	Solvents	Ratio solvents	Ziprasidone form
24	AcOH:EtOH:water	3:6:3	A
25	AcOH:EtOH	5:10	A
26	AcOH:EtOH	3:20	A
27	AcOH:EtOH	5:10	A
28	AcOH:water	5:15	A
29	HCOOH:MeOH	3:17	A
30	HCOOH:MeOH	3:10	A
31	HCOOH:MeOH:water	3:3:6	A
32	HCOOH:MeOH:water	6:6:12	A
33	HCOOH:MeOH:water	1.7:1.7:3	A
34	HCOOH:MeOH:water	3:6:3	A
35	HCOOH:MeOH:water		A

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences, Volume 95 may be used for guidance. All references mentioned herein are incorporated in their entirety.

What is claimed is:

1. Crystalline ziprasidone HCl, characterized by data selected from the group consisting of a powder XRD pattern with peaks at 10.9, 17.4 and 19.1  $\pm 0.2$  degrees 2 theta and an FTIR spectrum with peaks at about 3400, 3344, 3172, 2949, 970, 940, 872 and 843  $\text{cm}^{-1}$ .
2. The crystalline ziprasidone HCl of claim 1 characterized by a powder XRD pattern with peaks at 10.9, 17.4 and 19.1  $\pm 0.2$  degrees 2 theta.
3. The crystalline ziprasidone HCl of claim 2 further characterized by a powder XRD pattern with peaks at 25.0, 26.0  $\pm 0.2$  degrees 2 theta.
4. The crystalline ziprasidone HCl of claim 3 further characterized by a powder XRD pattern with peaks at 13.9, 20.6, 21.3, 21.8 and 23.0  $\pm 0.2$  degrees 2 theta.
5. The crystalline ziprasidone HCl of claim 4 characterized by powder XRD pattern substantially as depicted in figure 1.
6. The crystalline ziprasidone HCl of claim 1 characterized by an FTIR spectrum with peaks at 3400, 3344, 3172, 2949, 970, 940, 872 and 843  $\text{cm}^{-1}$ .
7. The crystalline ziprasidone HCl of claim 6 characterized by an FTIR spectrum substantially as depicted in figure 4.
8. The crystalline ziprasidone HCl of claim 1 containing less than about 5% of other polymorphic forms of ziprasidone HCl by weight.
9. The crystalline ziprasidone HCl of claim 1, wherein the crystalline ziprasidone HCl contains less than about 5% of Form M by weight.
10. The crystalline ziprasidone HCl of claim 1, having a water content of about 0.5% to about 6.6% by weight.
11. The crystalline ziprasidone HCl of claim 1, characterized by having high crystallinity.
12. The crystalline ziprasidone HCl of claim 11, wherein the crystallinity is as substantially depicted in figures 2 or 3.
13. The crystalline ziprasidone HCl of claim 1, characterized by having specific surface area higher than about 4 $\text{m}^2/\text{g}$  as measured by BET.
14. The crystalline ziprasidone HCl of claim 13, characterized by having specific surface area of about 5 to about 20 $\text{m}^2/\text{g}$ .
15. A process for preparing crystalline ziprasidone HCl of claim 1 comprising:

- a) providing a slurry of ziprasidone base, aqueous HCl and a solvent selected from the group consisting of toluene, monochlorobenzene, methanol, ethanol, diethyl-carbonate, water, isopropyl alcohol and mixtures thereof;
  - b) maintaining the slurry to obtain ziprasidone HCl of claim 1; and
  - 5 c) recovering the ziprasidone HCl of claim 1.
16. The process of claim 15, wherein the ziprasidone base is ziprasidone Form B.
17. The process of claim 15, wherein the temperature is at least about 40°C.
18. A process for preparing crystalline ziprasidone HCl of claim 1 comprising:
- a) dissolving ziprasidone base in a mixture of C<sub>1-4</sub> alcohol and an organic acid;
  - 10 b) adding aqueous HCl to the solution;
  - c) recovering the ziprasidone HCl.
19. The process of claim 18, wherein said C<sub>1-4</sub> alcohol is ethanol or methanol.
20. The process of claim 18 wherein said organic acid is a C<sub>1-4</sub> carboxylic acid.
21. The process of claim 19 wherein said organic acid is acetic acid or formic acid.
- 15 22. The process of claim 18, wherein the water content of the ziprasidone HCl of step (c) is raised by humidification.
23. A process for preparing crystalline ziprasidone HCl of claim 1 comprising:
- a) providing a slurry of ziprasidone HCl characterized by a powder XRD pattern of 7.4, 13.0, 20.7, 23.4, 25.9 ± 0.2 degrees 2 theta in THF or ethanol;
  - 20 b) maintaining the slurry to obtain the crystalline ziprasidone HCl of claim 1; and
  - c) recovering the crystalline ziprasidone HCl.
24. A process for preparing crystalline ziprasidone HCl of claim 1 comprising exposing ziprasidone HCl characterized by a powder XRD pattern of 7.4, 13.0,
- 25 20.7, 23.4, 25.9 ± 0.2 degrees 2 theta to a relative humidity of about 20% to about 60%.
25. A process for preparing the crystalline ziprasidone HCl of claim 1 substantially free of ziprasidone HCl Form M comprising:
- a) preparing a slurry of ziprasidone HCl in water, optionally in the presence of
  - 30 an organic solvent, at a temperature of about 0°C to about 40°C;
  - b) maintaining the slurry to obtain the crystalline ziprasidone HCl; and
  - c) recovering the ziprasidone HCl.



- wherein the slurry is prepared by combining aqueous HCl in less than about 30 minutes with ziprasidone base in water.
26. The process of claim 25, wherein the combining is carried out in less than about 20 minutes.
- 5 27. The process of claim 26, wherein the combining is carried out in less than about 10 minutes.
28. The process of claim 27, wherein the ziprasidone HCl obtained in step (c) contains NMT about 5% of Form M.
29. The process of claim 25, wherein the solvent is a linear or branched C<sub>1</sub> to C<sub>4</sub>  
10 alcohol.
30. The process of claim 29, wherein the alcohol is isopropyl alcohol.
31. The process of claim 30, wherein the alcohol has a ratio of about 2:1 to about 0:20 volume of the alcohol to volume of water.
32. The process of claim 25, wherein the HCl is added in about 2 to about 8  
15 equivalents.
33. Crystalline ziprasidone HCl prepared by the process of claim 15, 18, 23, 24 or 25.
34. A process for preparing ziprasidone HCl Form M comprising heating a slurry of the crystalline ziprasidone HCl of claim 1 in ethanol.
35. The crystalline ziprasidone HCl of claim 1, of which no more than about 5%  
20 transform to Form M upon heating to a temperature of up to about 140°C.
36. Solid crystalline ziprasidone HCl having a water content of about 4.6% to about 6.6% by weight.
37. The crystalline ziprasidone HCl of claim 1, of which no more than about 5% transform to Form M upon storage at 0% relative humidity for at least 20 days.
- 25 38. The crystalline ziprasidone HCl of any one of claims 1 or 37, of which no more than about 5% transform to Form M upon storage at a temperature of about 25 to 55°C for at least 3 months.
39. The crystalline ziprasidone HCl of claim 38, wherein no more than about 5% transform to Form M upon storage at a temperature of from about 25 to 55°C for  
30 at least 6 months.
40. The crystalline ziprasidone HCl of claim 36, having specific surface area higher than about 4m<sup>2</sup>/g.

41. The crystalline ziprasidone HCl of claim 40, characterized by having specific surface area of about 5 to about 20m<sup>2</sup>/g.
42. A pharmaceutical composition comprising crystalline ziprasidone HCl of claim 36 and a pharmaceutically acceptable excipient.
- 5 43. A method of treating a patient suffering from schizophrenia comprising administering to the patient the pharmaceutical composition of claim 42.
44. A pharmaceutical composition comprising an effective amount of the crystalline ziprasidone HCl having a powder XRD pattern with peaks at about 10.9, 17.4 and 19.1, 25.0, 26.0  $\pm$ 0.2 degrees 2 theta.
- 10 45. Solid crystalline ziprasidone HCl sesquihydrate.
46. A pharmaceutical composition of ziprasidone HCl prepared by a process comprising:
- a) providing crystalline ziprasidone HCl of any of claim 36 or 45;
- b) admixing the ziprasidone HCl with at least a single pharmaceutically acceptable excipient.
- 15 47. Solid crystalline ziprasidone HCl having specific surface area higher than about 4m<sup>2</sup>/g.
48. The crystalline ziprasidone HCl of claim 47, characterized by having specific surface area of about 5 to about 20m<sup>2</sup>/g.
- 20 49. A pharmaceutical composition of ziprasidone HCl prepared by a process comprising:
- a) providing crystalline ziprasidone HCl of claim 47;
- b) admixing the ziprasidone HCl with at least a single pharmaceutically acceptable excipient.
- 25 50. A method of treating a patient suffering from schizophrenia comprising administering to the patient the pharmaceutical composition of any one of claims 44 or 49.

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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM A

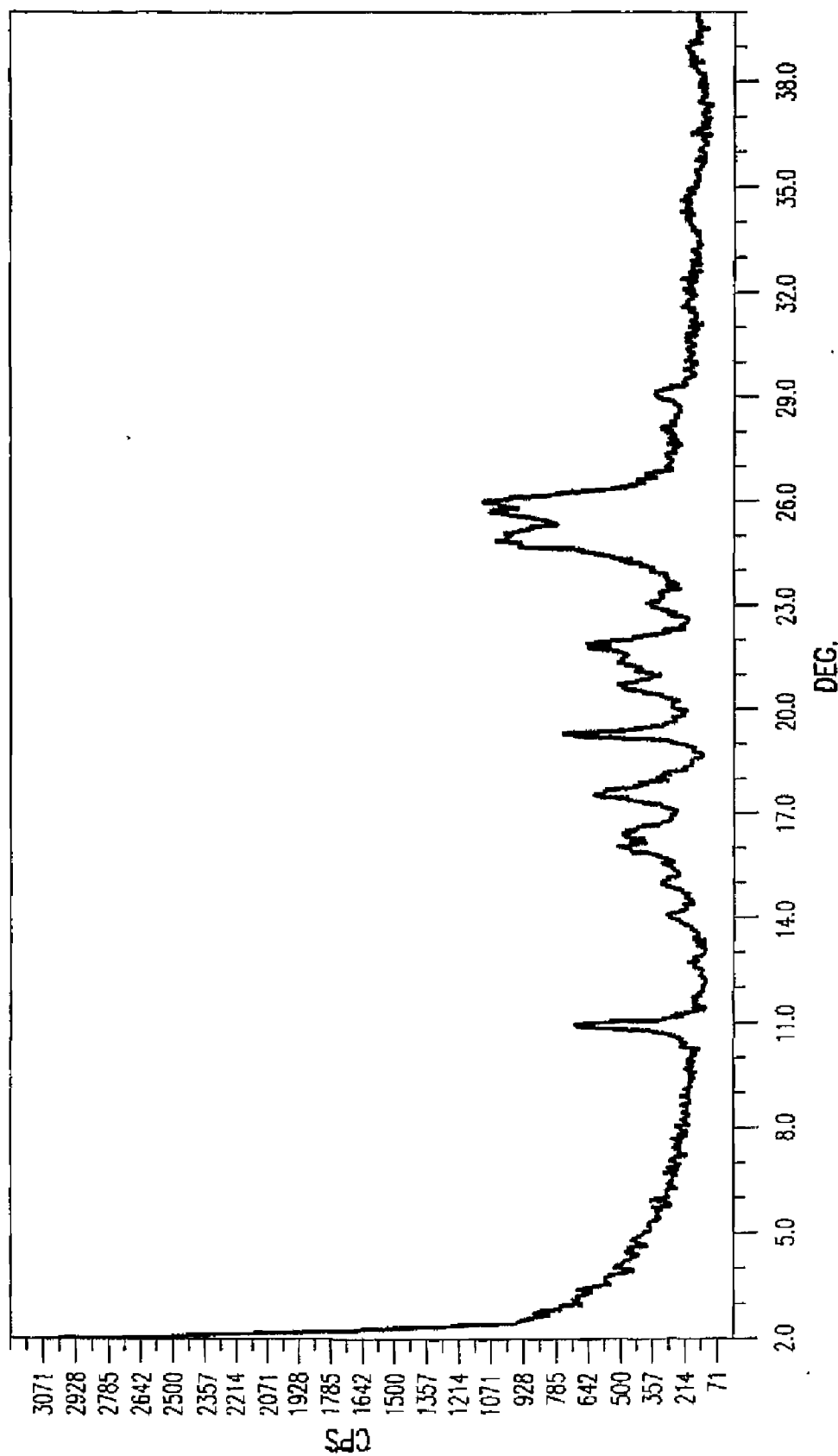


FIG.1

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X-RAY POWDER DIFFRACTOGRAM: HIGH CRYSTALLINITY ZIPRASIDONE HCl FORM A, CONTAINING ABOUT 5%  
FORM M

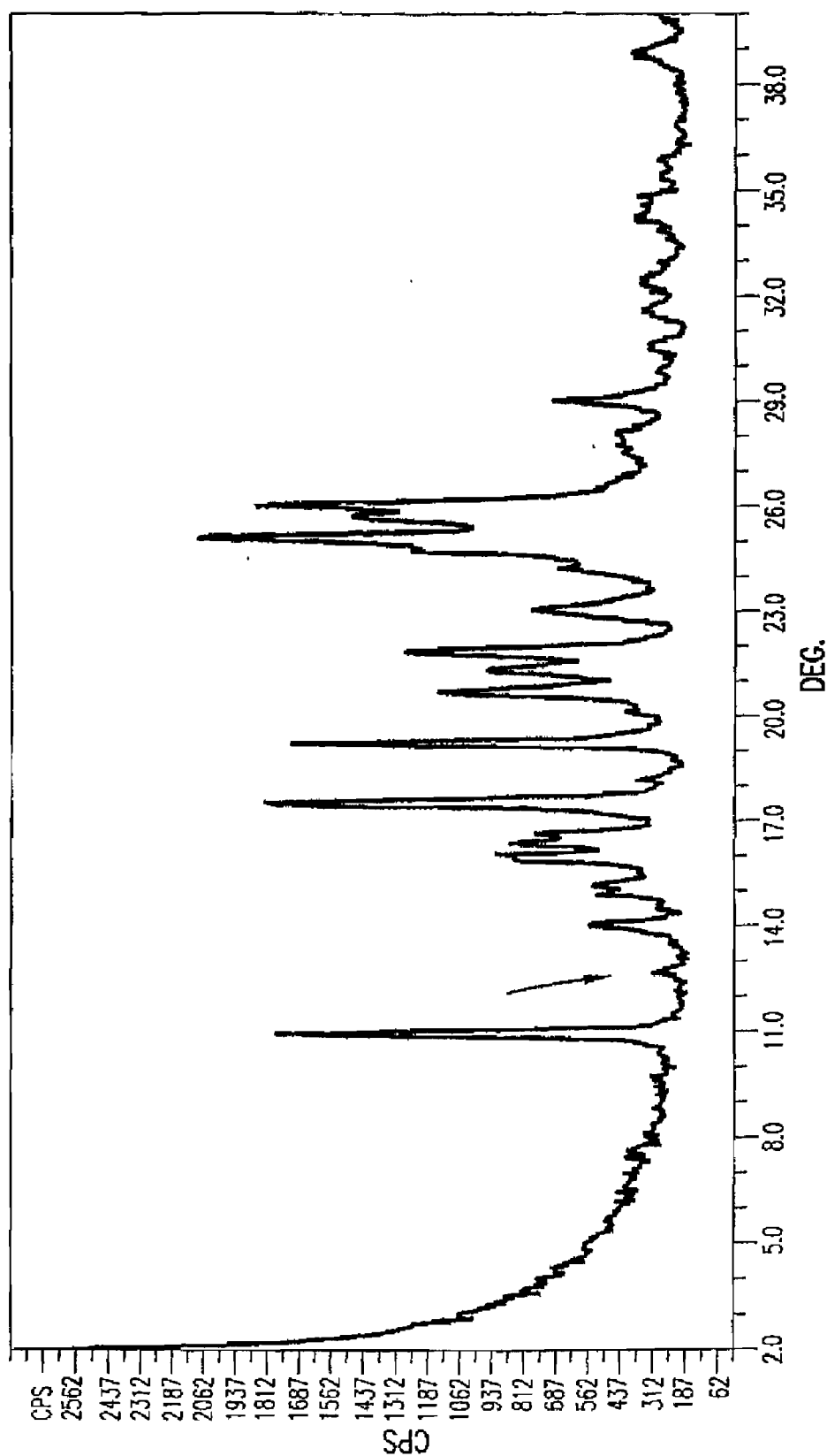


FIG. 2

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## X-RAY POWDER DIFFRACTOGRAM: HIGH CRYSTALLINITY ZIPRASIDONE HCl FORM A

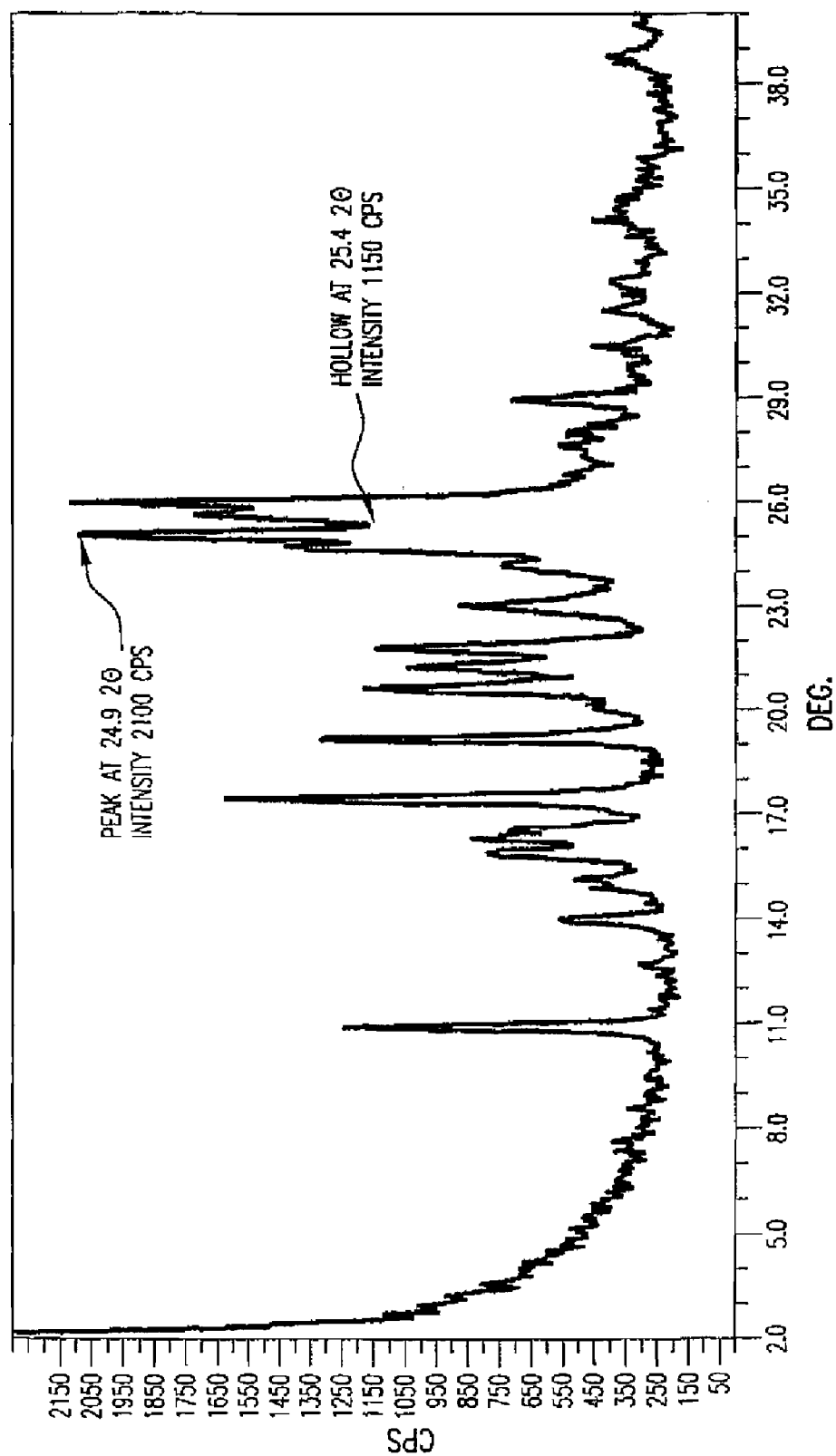


FIG. 3

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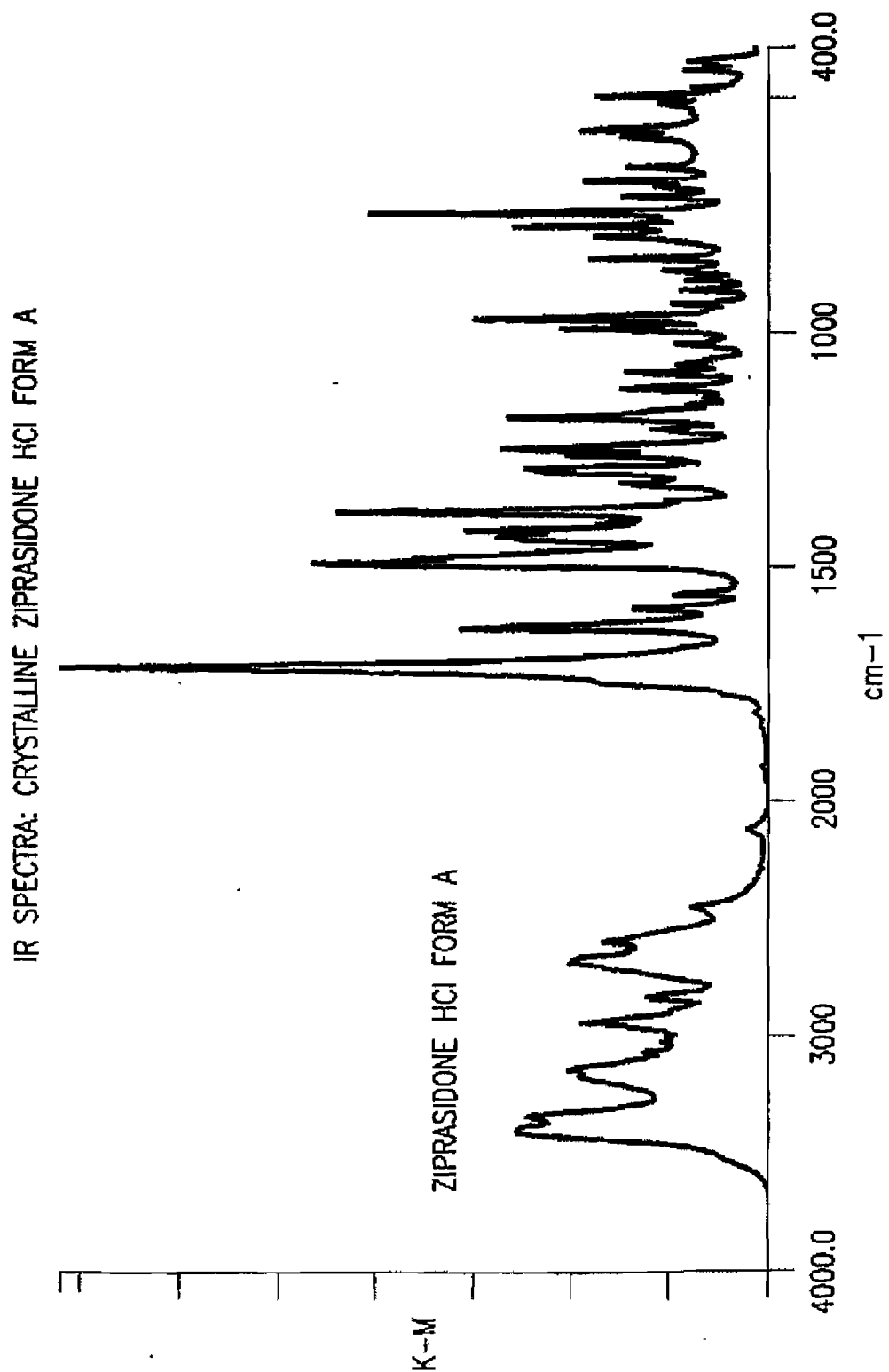


FIG.4

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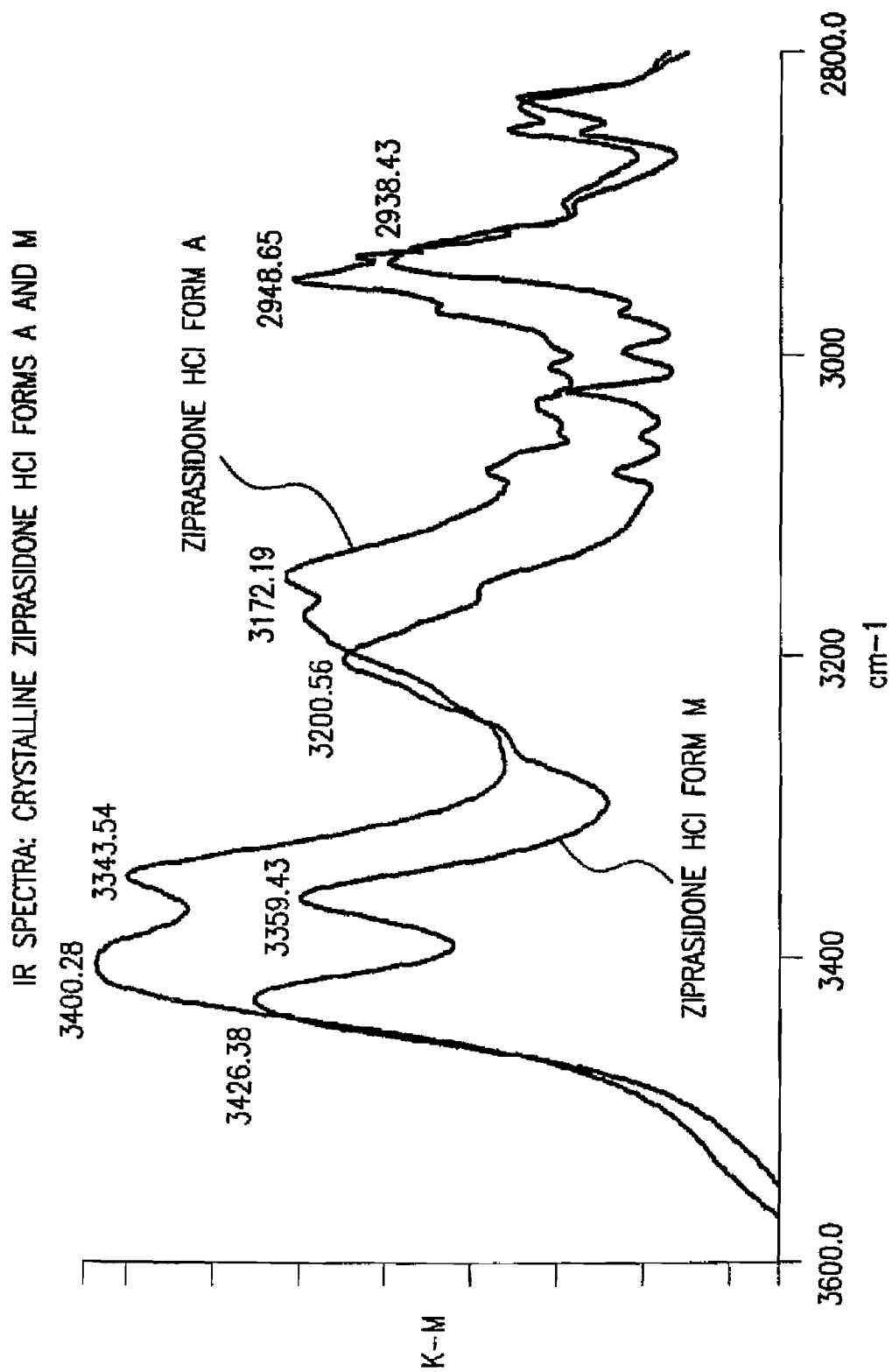


FIG.5

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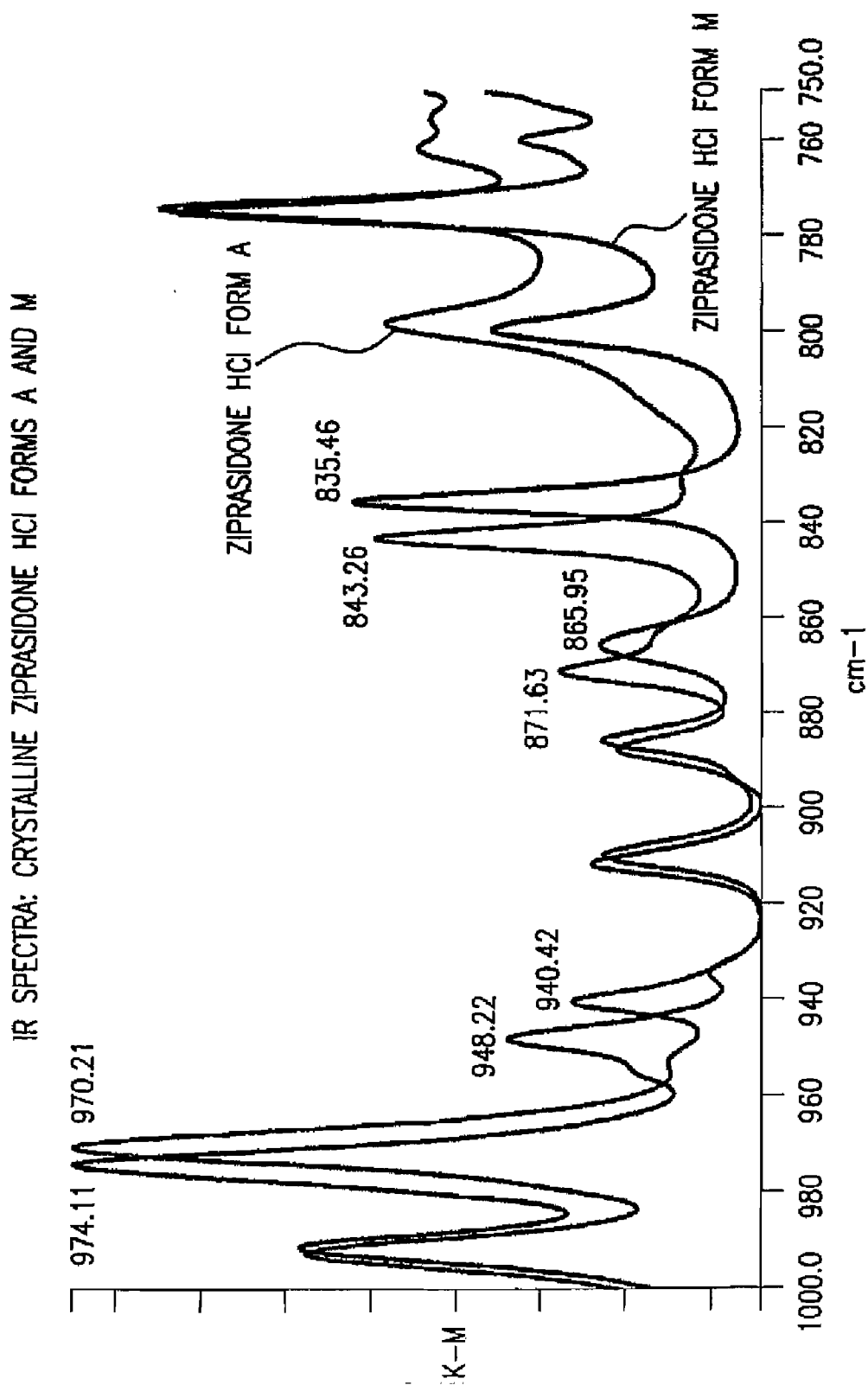


FIG. 6



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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM A

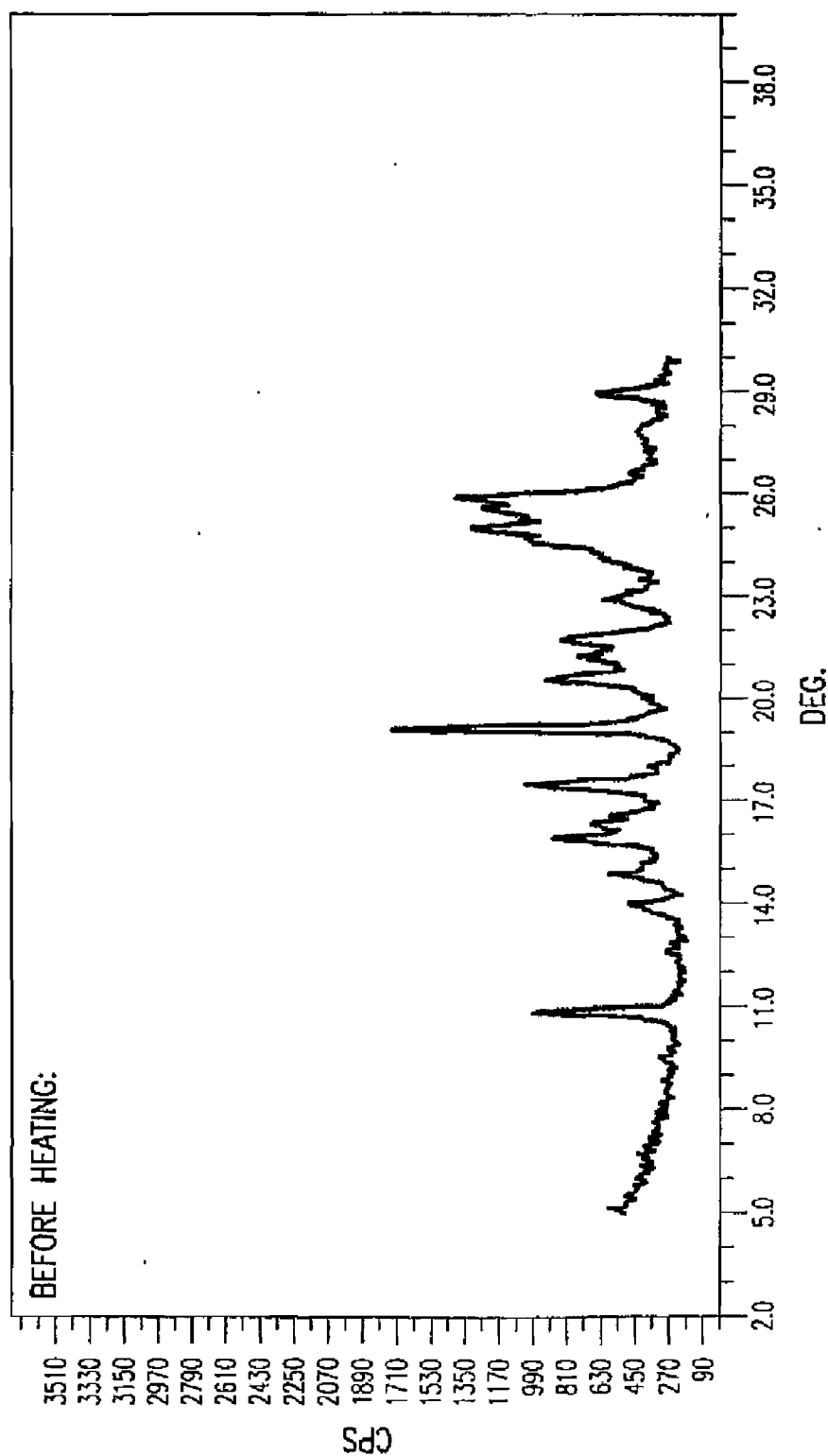


FIG. 7A

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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM A

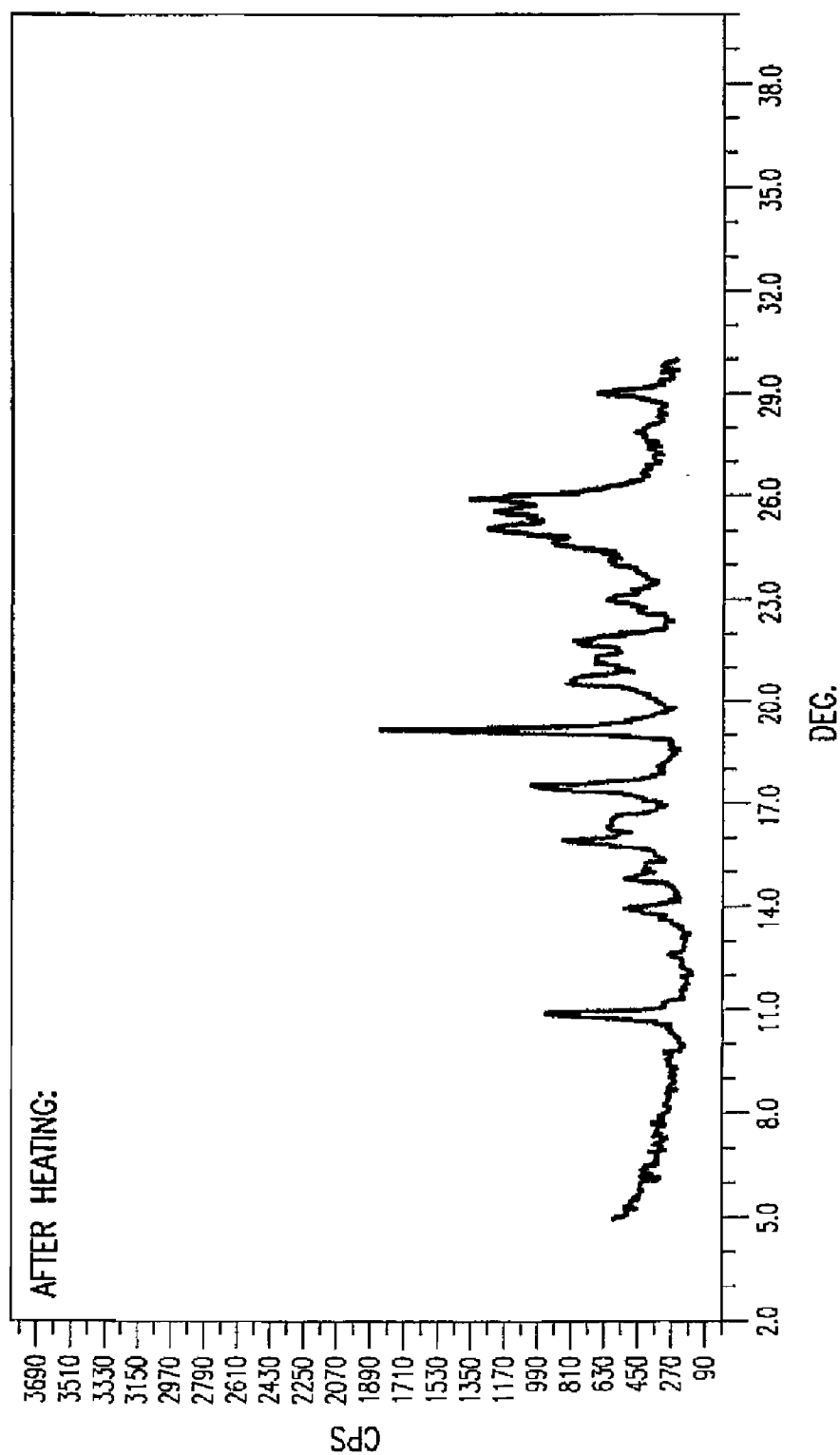


FIG. 7B

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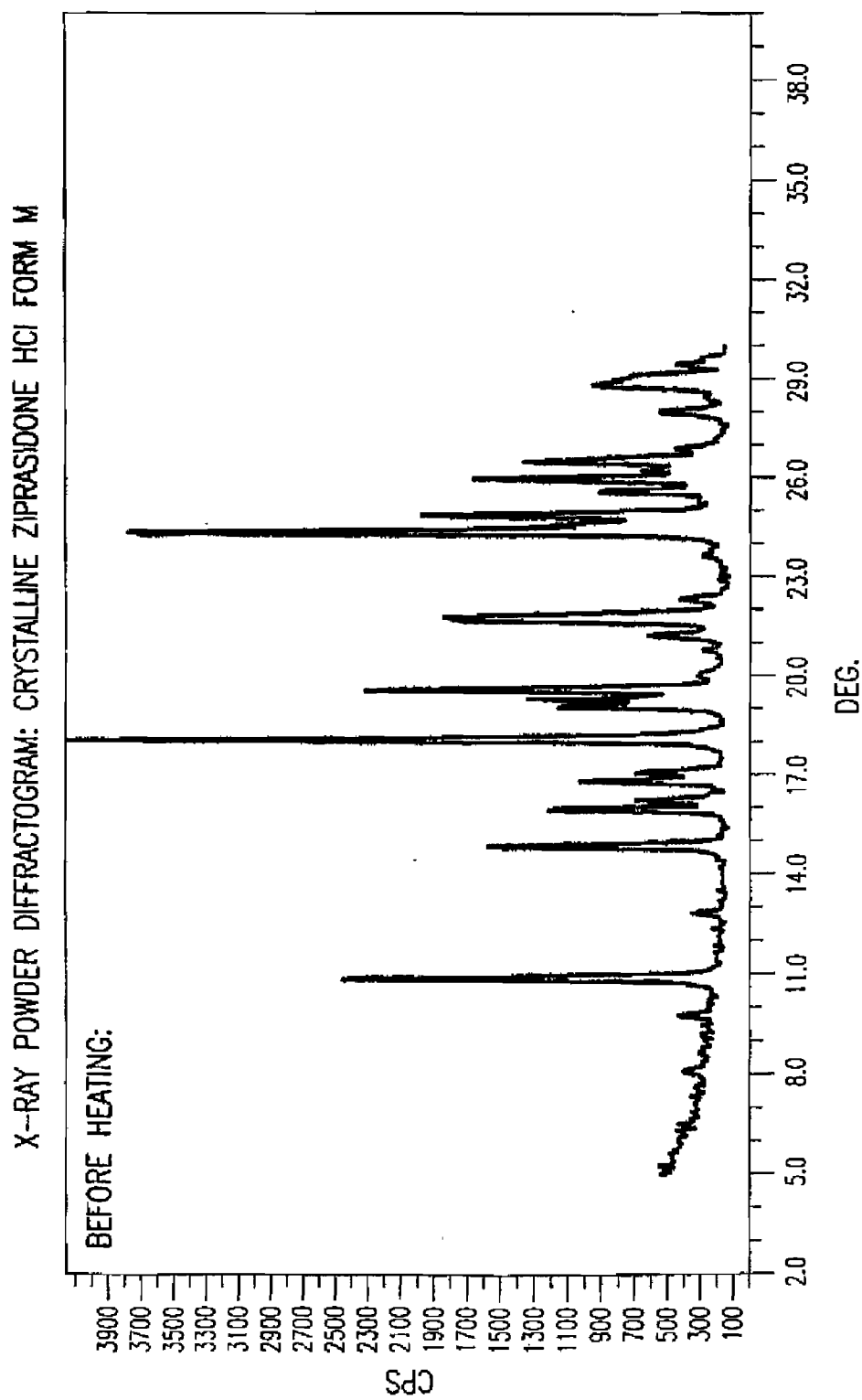


FIG. 8A

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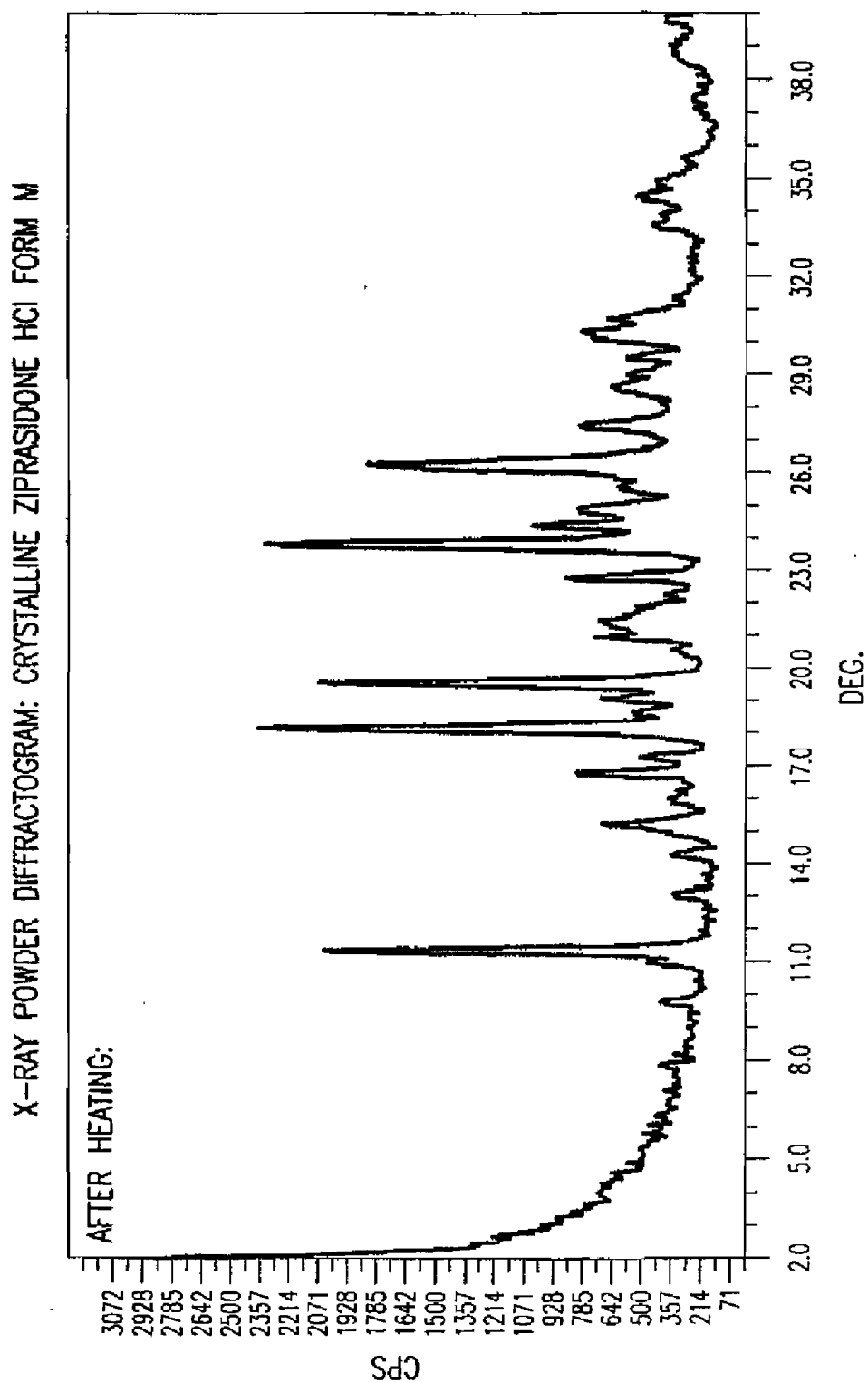


FIG.8B

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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM A BEFORE STORAGE  
AT 0% RELATIVE HUMIDITY

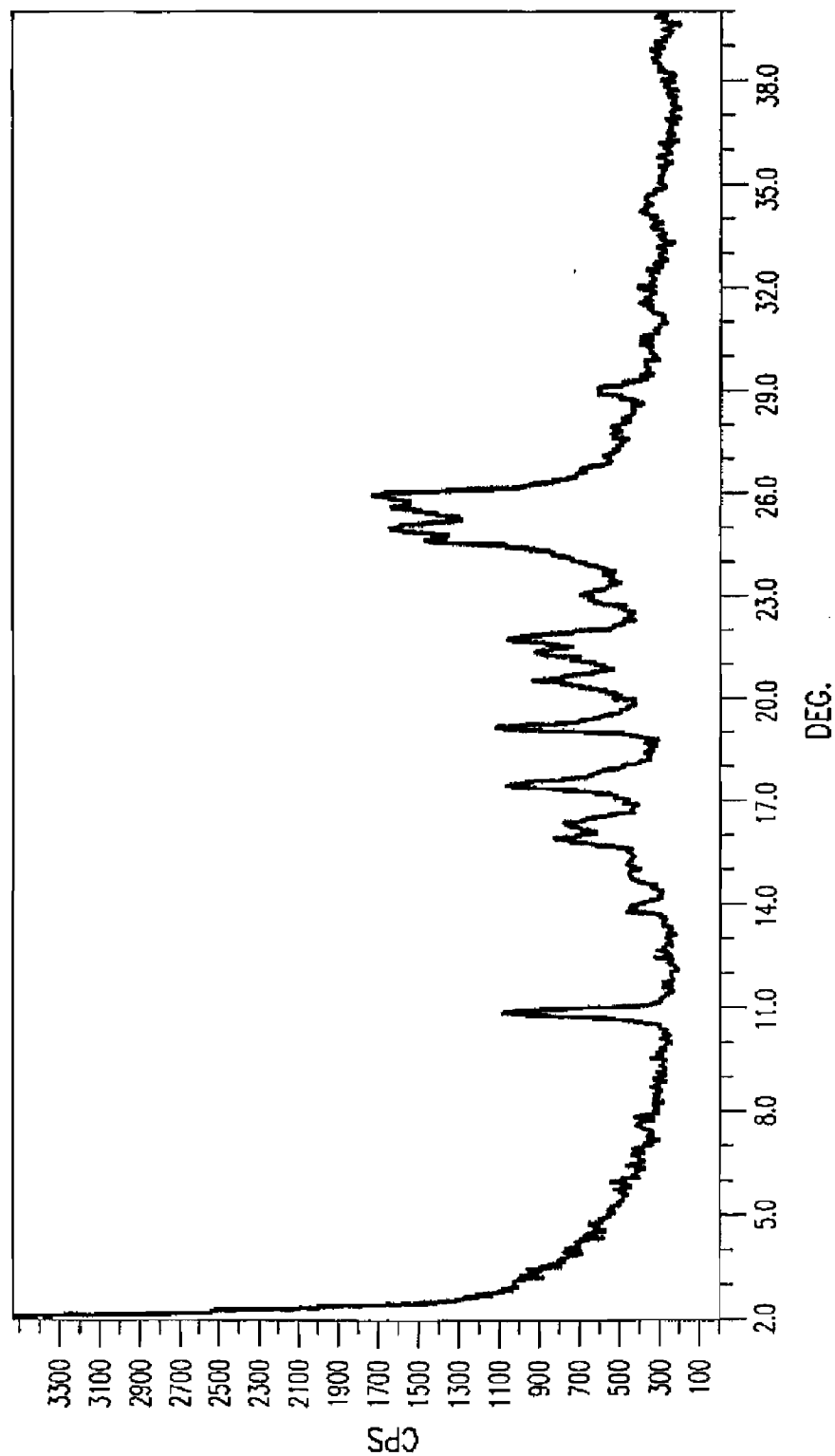


FIG. 9A

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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM A  
AFTER 22 DAYS OF STORAGE AT 0% RELATIVE HUMIDITY

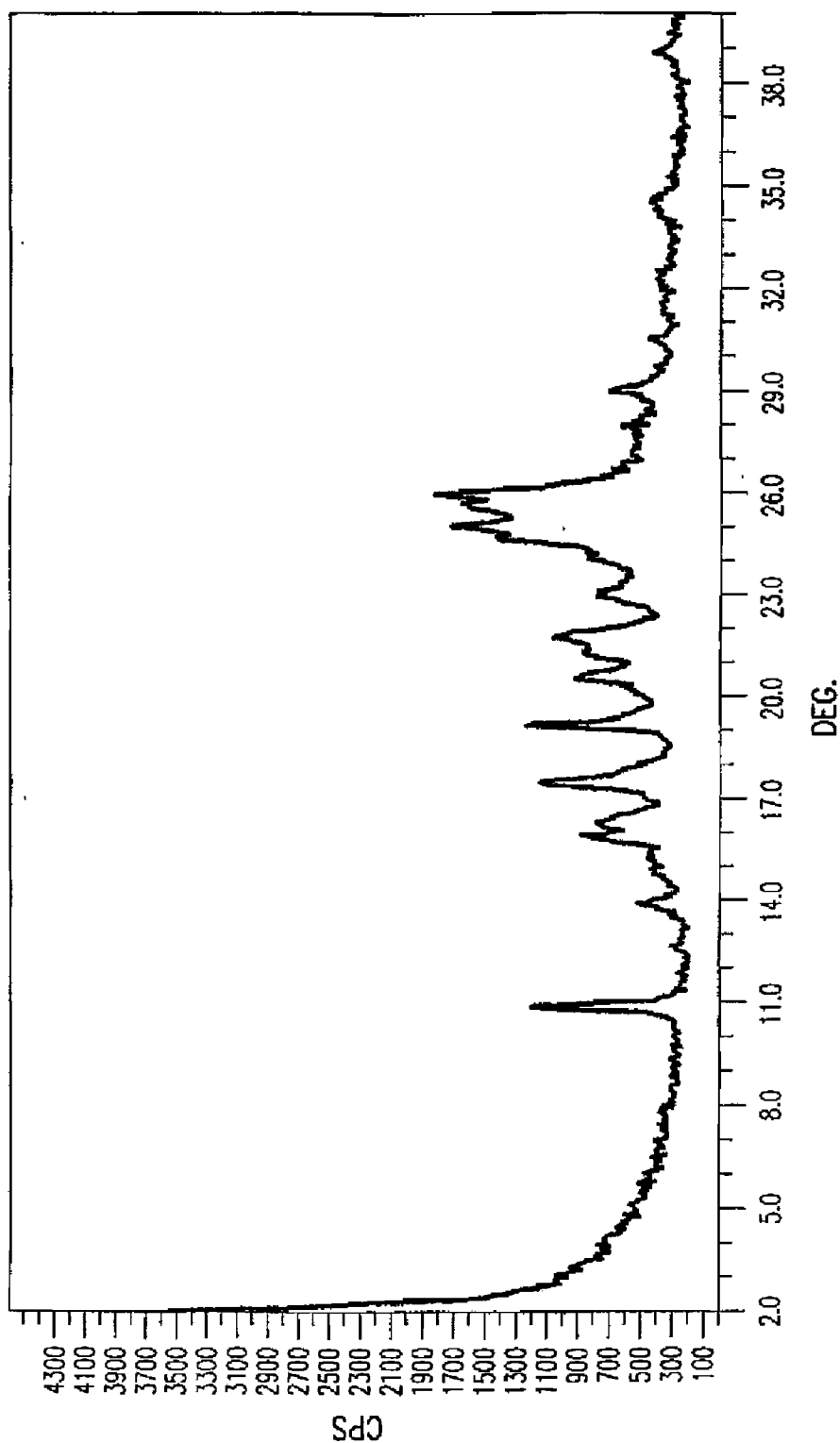


FIG. 9B

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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM M  
BEFORE STORAGE AT 0% RELATIVE HUMIDITY:

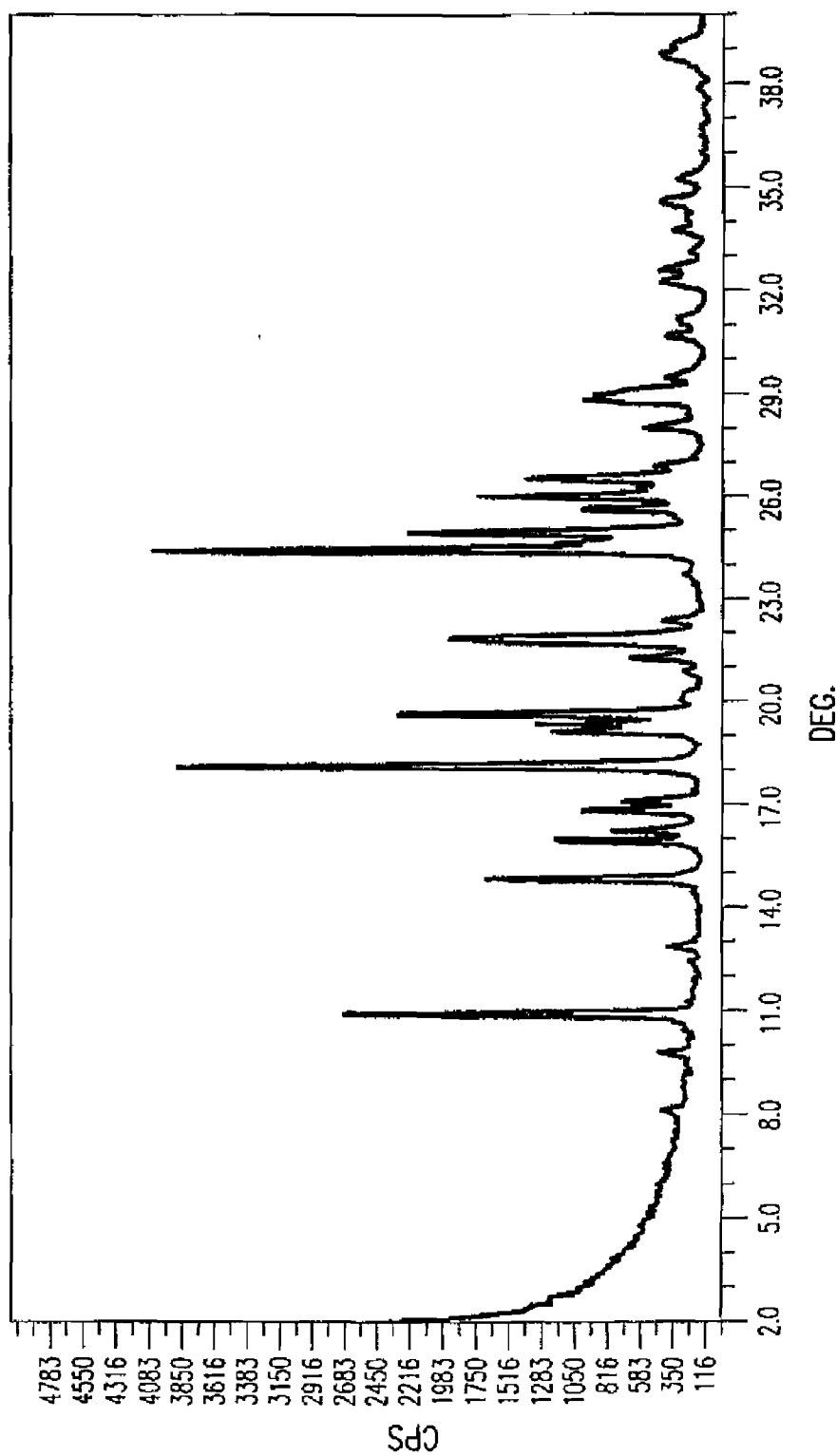


FIG. 10A

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X-RAY POWDER DIFFRACTOGRAM: CRYSTALLINE ZIPRASIDONE HCl FORM M  
AFTER 7 DAYS OF STORAGE AT 0% RELATIVE HUMIDITY:

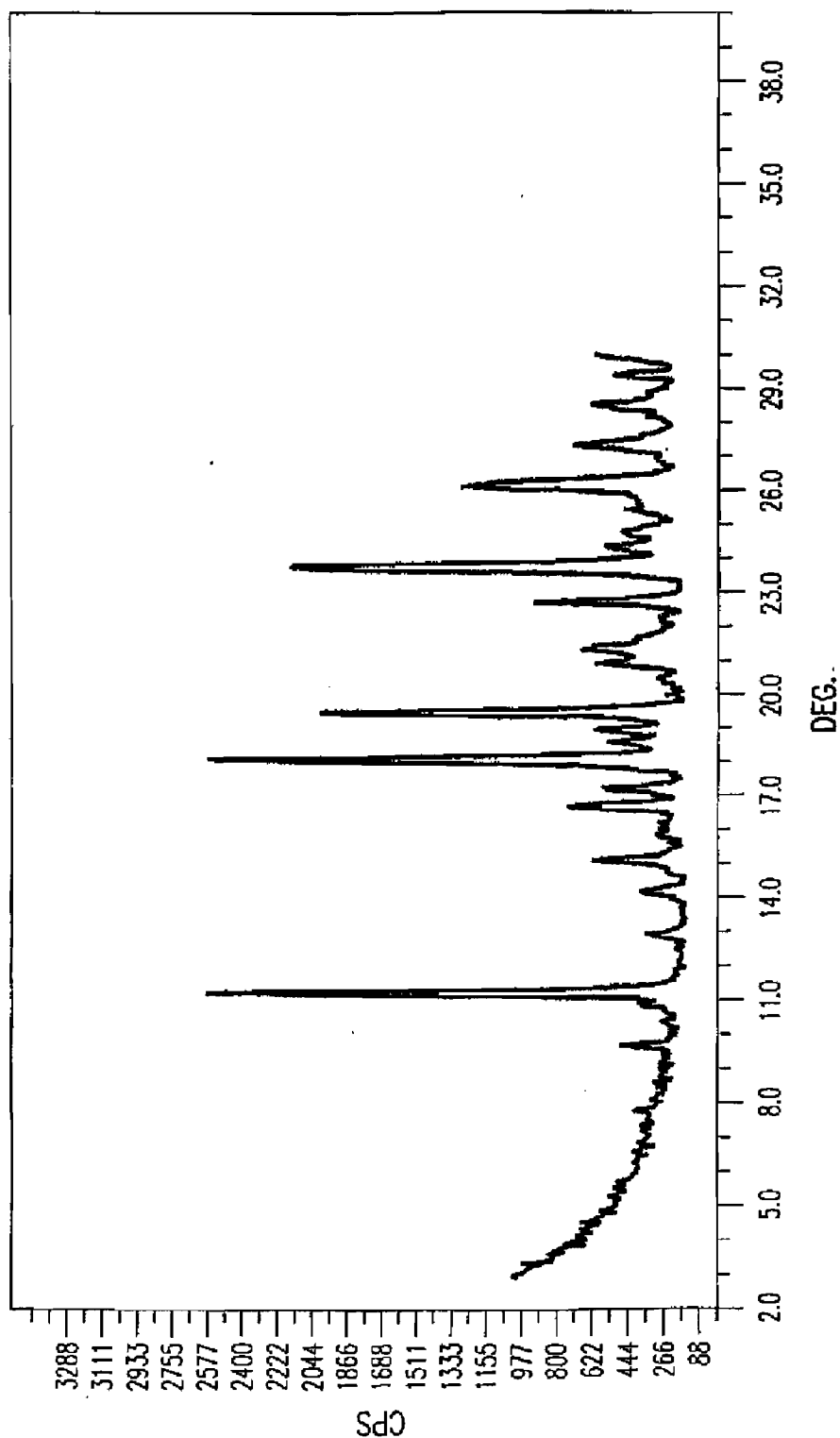


FIG. 10B



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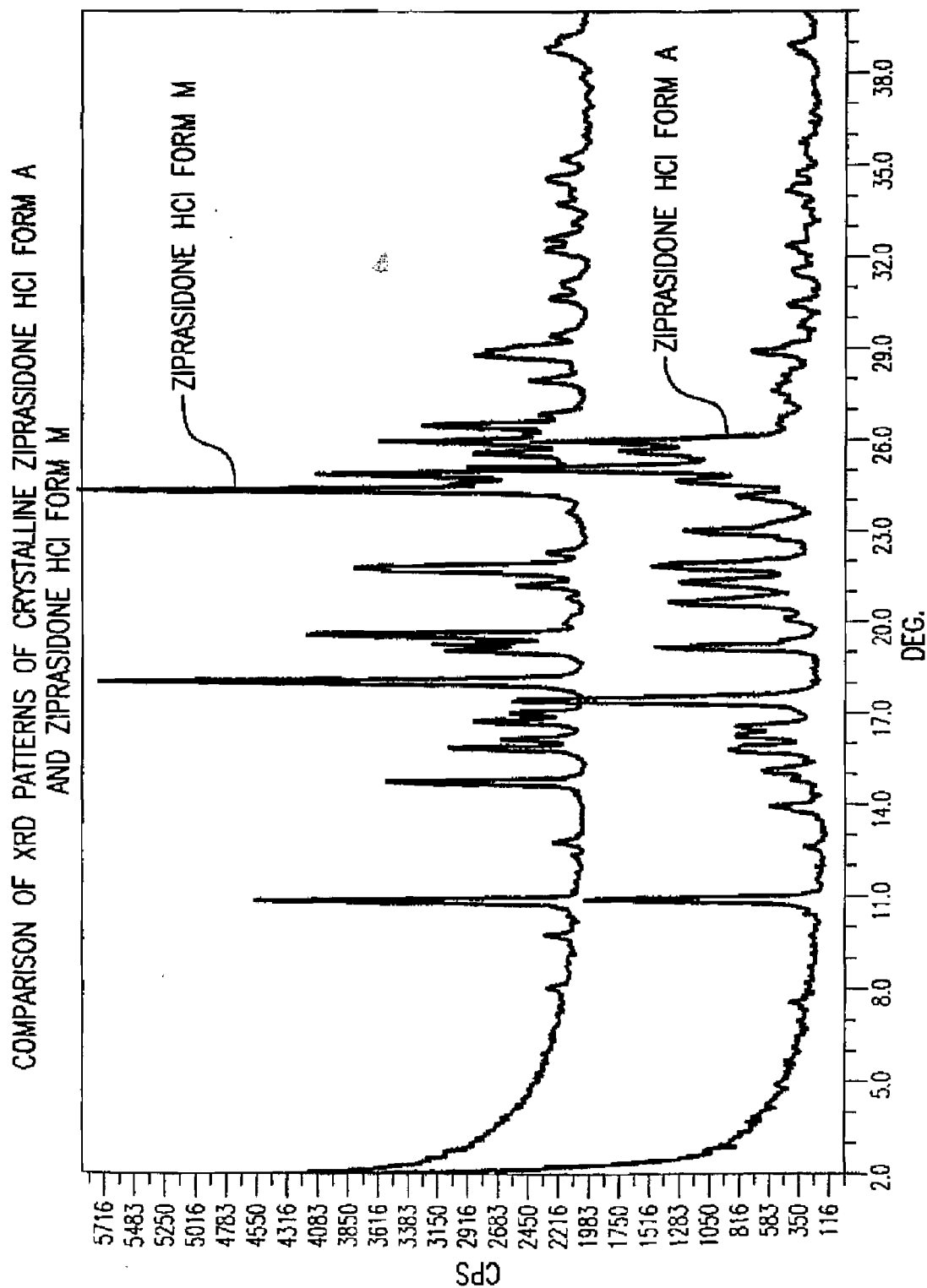


FIG.11